(19)日本国特許庁（ＪＰ）　(12)公開特許公報（Ａ）　(11)特許出願公開番号
特開平11－147819
(43)公開日　平成11年(1999)６月２日

(51)Int.Cl.[6]	識別記号	ＦＩ	
Ａ６１Ｋ　9/28		Ａ６１Ｋ　9/28	Ｚ
47/00		47/00	

審査請求　未請求　請求項の数20　ＯＬ　（全 14 頁）

(21)出願番号　特願平10－256164
(22)出願日　平成10年(1998)９月10日
(31)優先権主張番号　特願平9－245778
(32)優先日　平９(1997)９月10日
(33)優先権主張国　日本（ＪＰ）

(71)出願人　000002934
武田薬品工業株式会社
大阪府大阪市中央区道修町四丁目１番１号
(72)発明者　福田　誠人
奈良県奈良市鶴舞西町２番10－Ｂ－508号
(72)発明者　伊藤　弘樹
大阪府吹田市上山田７番Ｄ－304号
(74)代理人　弁理士　朝日奈　忠夫　（外１名）

(54)【発明の名称】　安定化された医薬製剤

(57)【要約】
【課題】光、とりわけ紫外線や熱に対して安定であり、保存安定性に優れた医薬製剤を提供する。
【解決手段】紫外線によりフリーラジカルを発生しうる遮光剤、およびフリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤。

1

【特許請求の範囲】

【請求項１】(i)紫外線によりフリーラジカルを発生しうる遮光剤、および(ii)フリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤。

【請求項２】被覆剤が、さらにエステル類およびアルコール類から選ばれる油状物質を含有してなる請求項１記載の医薬製剤。

【請求項３】紫外線によりフリーラジカルを発生しうる遮光剤が金属酸化物である請求項１記載の医薬製剤。

【請求項４】金属酸化物が酸化チタン，三二酸化鉄または酸化亜鉛である請求項３記載の医薬製剤。

【請求項５】フリーラジカル消去剤が亜硫酸塩またはビタミン類である請求項１記載の医薬製剤。

【請求項６】ビタミン類がビタミンＣ類またはビタミンＥ類である請求項５記載の医薬製剤。

【請求項７】油状物質がポリエチレングリコールである請求項２記載の医薬製剤。

【請求項８】（i）酸化チタンおよび（ii）亜硫酸水素ナトリウム，アスコルビン酸，アスコルビン酸ナトリウム，アスコルビン酸カルシウム，ｄｌ－α－トコフェロールまたは酢酸ｄｌ-α－トコフェロールを含有する被覆剤で被覆してなる安定化された医薬製剤。

【請求項９】被覆剤が、さらに塩基性物質を含有する請求項２記載の医薬製剤。

【請求項１０】塩基性物質が金属の炭酸塩または金属水酸化物である請求項９記載の医薬製剤。

【請求項１１】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤。

【請求項１２】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤で被覆してなる安定化された医薬製剤。

【請求項１３】被覆剤が、さらに紫外線によりフリーラジカルを発生しうる遮光剤を含有してなる請求項１２の医薬製剤。

【請求項１４】(i)紫外線によりフリーラジカルを発生しうる遮光剤、および(ii)フリーラジカル消去剤を含有することを特徴とする被覆剤。

【請求項１５】(i)紫外線によりフリーラジカルを発生しうる遮光剤、および(ii)フリーラジカル消去剤を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法。

【請求項１６】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法。

【請求項１７】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法。

2

【請求項１８】(i)紫外線によりフリーラジカルを発生しうる遮光剤、および(ii)フリーラジカル消去剤を含有する被覆剤の医薬製剤安定化のための使用。

【請求項１９】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤の医薬製剤安定化のための使用。

【請求項２０】（i）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤の医薬製剤安定化のための使用。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、光（とりわけ紫外線）や熱に対して安定であり、保存安定性に優れた医薬製剤、およびこのような医薬製剤の原料である被覆剤に関する。

【０００２】

【従来の技術】ホルムアルデヒド（ポリエチレングリコール400の不純物として含まれるもの、およびポリエチレングリコール400の空気酸化により生じるものを含む）とO^6－ベンジルグアニンとが反応することにより、O^6－ベンジルグアニンがポリエチレングリコール400水溶液中、室温下で分解することが知られている〔ファーマシューチカル・リサーチ（Pharmaceutical Research）、11巻、７号、1060－1064頁、1994年〕。酸化チタンおよびポリエチレングリコール6000を含有する腸溶性フィルム液を用いて腸溶性コーティングを行うことが特開昭６３－３０１８１６（ＥＰ公開第０２７７７４１号）に記載されている。ビタミンＣ、インキョー（Ｙｉｎｑｉａｏ）抽出物、アセトアミノフェン、クロルフェニラミン、炭酸カルシウム、デンプン、デキストラン、ペパーミント油、インキョー（Ｙｉｎｑｉａｏ）およびジンファン（ｊｉｎｇｆａｎｇ）の揮発性油を有する錠剤をヒドロキシプロピルメチルセルロース、Ｎｏ２ 腸溶性ビニル樹脂、ＰＥＧ６０００、ごま油、ツイーン８０、タルク、酸化チタン、ステアリン酸マグネシウム、フードカラー、９５％エタノール、蒸留水を含む成分で被覆された錠剤がケミカル アブストラクツ １２２：２３８８５３に記載されている。特開昭６３－１６６８２４は、光不安定な薬物含有油性溶液を、少なくとも８５％が粒子径０．１μｍ以下の微粒子酸化チタンを含有する剤皮で被覆された軟カプセル剤を開示している。

【０００３】

【発明が解決しようとする課題】光に対して不安定な医薬製剤を消費者に提供する場合、医薬製剤の遮光包装または遮光被覆を行う必要がある。しかしながら、病院内の薬局あるいは患者側での医薬製剤の保存状態を考慮すれば、遮光包装で医薬製剤の品質を十分保証できるとは言い難い。したがって、光に対して不安定な医薬製剤を

製造する場合には、遮光被覆を行うことが望まれる。ところが、光に対して不安定な薬物の製剤化に際し、酸化チタンなどの遮光剤とポリエチレングリコールなどの可塑剤とを含む被覆剤を、薬物含有錠剤に被覆したところ、得られるフィルムコーティング錠が、被覆処理を行う前の錠剤よりも、光に対する安定性において劣るという問題点が判明した。

【０００４】

【課題を解決するための手段】このような問題点に鑑み、フィルムコーティング錠中での薬物の安定化について検討したところ、１）紫外線により被覆剤中の酸化チタンがフリーラジカルを発生すること、２）フリーラジカルによって薬物や被覆剤中のポリエチレングリコール等のアルコール類が分解すること、３）被覆剤中でポリエチレングリコール等のアルコール類の分解物、例えばホルムアルデヒド，アセトアルデヒドなどのアルデヒド類、ギ酸などの酸や、過酸化物がさらに薬物の分解を引き起こすことを見いだした。このような知見に基づいて、さらに薬物不安定化要因を解消し、種々の安定化された医薬製剤を得るべく検討した結果、本発明を完成した。すなわち、本発明は、

（１）（ｉ）紫外線によりフリーラジカルを発生しうる遮光剤、および(ii)フリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤；

（２）被覆剤が、さらにエステル類およびアルコール類から選ばれる油状物質を含有してなる上記（１）記載の医薬製剤；

（３）紫外線によりフリーラジカルを発生しうる遮光剤が金属酸化物である上記（１）記載の医薬製剤；

（４）金属酸化物が酸化チタン，三二酸化鉄または酸化亜鉛である上記（３）記載の医薬製剤；

（５）フリーラジカル消去剤が亜硫酸塩またはビタミン類である上記（１）記載の医薬製剤；

（６）ビタミン類がビタミンＣ類またはビタミンＥ類ある上記（５）記載の医薬製剤；

（７）油状物質がポリエチレングリコールである上記（２）記載の医薬製剤；

（８）（ｉ）酸化チタンおよび（ii）亜硫酸水素ナトリウム，アスコルビン酸，アスコルビン酸ナトリウム，アスコルビン酸カルシウム，ｄｌ－α－トコフェロールまたは酢酸ｄｌ-α－トコフェロールを含有する被覆剤で被覆してなる安定化された医薬製剤；

（９）被覆剤が、さらに塩基性物質を含有する上記（２）記載の医薬製剤；

（１０）塩基性物質が金属の炭酸塩または金属水酸化物である上記（９）記載の医薬製剤。

（１１）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤；

（１２）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤で被覆してなる安定化された医薬製剤；

（１３）被覆剤が、さらに紫外線によりフリーラジカルを発生しうる遮光剤を含有してなる上記（１２）の医薬製剤；

（１４）（ｉ）紫外線によりフリーラジカルを発生しうる遮光剤、および（ii）フリーラジカル消去剤を含有することを特徴とする被覆剤；

（１５）（ｉ）紫外線によりフリーラジカルを発生しうる遮光剤、および（ii)フリーラジカル消去剤を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法；

（１６）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法；

（１７）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤で、薬物含有組成物を被覆することを特徴とする医薬製剤の安定化方法；

（１８）（ｉ）紫外線によりフリーラジカルを発生しうる遮光剤、および（ii）フリーラジカル消去剤を含有する被覆剤の医薬製剤安定化のための使用；

（１９）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）フリーラジカル消去剤を含有する被覆剤の医薬製剤安定化のための使用；および、

（２０）（ｉ）エステル類およびアルコール類から選ばれる油状物質、および（ii）塩基性物質を含有する被覆剤の医薬製剤安定化のための使用に関する。

【０００５】以下に、本発明において用いられる「紫外線によりフリーラジカルを発生しうる遮光剤」、「フリーラジカル消去剤」、「エステル類およびアルコール類から選ばれる油状物質」、「塩基性物質」、「被覆剤」および「医薬製剤」について詳述する。

【０００６】「紫外線によりフリーラジカルを発生しうる遮光剤」は、遮光を目的として医薬製剤中に添加され、かつ紫外線によりフリーラジカルを発生しうるものを意味する。一般にこれら遮光剤は、常温で、室内の蛍光灯下あるいは屋外の日光下にさらすことによりフリーラジカルを発生するものを意味する。フリーラジカルとしては、例えば$HO\cdot$、$HO_2\cdot$、$O_2\cdot^-$などが挙げられる。このような遮光剤としては、例えば酸化チタン、三二酸化鉄、酸化亜鉛等の無機物の酸化物が挙げられる。遮光剤は、好ましくは金属酸化物であり、さらに好ましくは酸化チタンである。また、酸化チタンを用いる場合、その粒子径は、通常、約０．０１～約１．５μｍ、好ましくは約０．１～約０．７μｍである。「紫外線によりフリーラジカルを発生しうる遮光剤」の被覆剤中の含量は、医薬製剤の遮光という目的を達成し得る量であればよく、例えば約５～約３０重量%、好ましくは

約１０～約３０重量％である。

【０００７】「フリーラジカル消去剤」は、前記したフリーラジカルを消去しうる物質、および酸化反応による被覆剤成分あるいは医薬製剤成分の分解を抑制する物質であればよい。フリーラジカル消去剤としては、例えばマンニトール等の糖アルコール類；安息香酸等の有機酸；トリプトファン、システイン等のアミノ酸；炭酸イオン；銅錯体、マンガン錯体等の金属錯体；亜硫酸水素ナトリウム、亜硫酸ナトリウム、メタ重亜硫酸ナトリウム等の亜硫酸塩；ナトリウムホルムアルデヒドスルホキシレート（ロンガリット）、チオグリセロール等のチオール誘導体；グアヤク脂等の天然樹脂；ノルジヒドログアヤレチック酸、没食子酸プロピル、ブチルヒドロキシアニソール、ジブチルヒドロキシトルエン等のフェノール誘導体；エリソルビン酸、エリソルビン酸ナトリウム、ビタミンC類（例、アスコルビン酸パルミテート，アスコルビン酸ジパルミテート，アスコルビン酸ステアレート等のアスコルビン酸エステル、アスコルビン酸ナトリウム，アスコルビン酸カルシウム等のアスコルビン酸塩）、ビタミンE類（例、コハク酸ｄｌ－α－トコフェロール，コハク酸ｄ－α－トコフェロール，コハク酸ｄｌ－α－トコフェロールカルシウム，酢酸ｄｌ－α－トコフェロール，酢酸ｄ－α－トコフェロール、ニコチン酸ｄｌ－α－トコフェロール等のトコフェロールのエステル類、ｄｌ－α－トコフェロール、ｄ－α－トコフェロール、ｄｌ－δ－トコフェロール、ｄ－δ－トコフェロール、天然ビタミンE）、β－カロチン等のビタミン類；グルタチオン等のペプチド；尿酸等のプリン誘導体などが挙げられる。これらのフリーラジカル消去剤は、１種または２種以上を適宜の割合で混合して用いてもよい。「フリーラジカル消去剤」は、好ましくは亜硫酸塩またはビタミン類（とりわけビタミンC類、ビタミンE類）であり、さらに好ましくは亜硫酸水素ナトリウム、アスコルビン酸、アスコルビン酸ナトリウム、アスコルビン酸カルシウム、ｄｌ－α－トコフェロールまたは酢酸ｄｌ－α－トコフェロールである。また、「フリーラジカル消去剤」の作用を増強するために、エチレンジアミン四酢酸またはその塩等を併用してもよい。「フリーラジカル消去剤」の被覆剤中の含量は、被覆剤に含まれる「紫外線によりフリーラジカルを発生しうる遮光剤」から発生したフリーラジカルを消去できる量であればよい。「フリーラジカル消去剤」の被覆剤中の含量は、例えば約０．１～約５０重量％、好ましくは約１～約２０重量％である。

【０００８】「エステル類およびアルコール類から選ばれる油状物質」としては、例えば約２０～約６５℃で油状のエステル類およびアルコール類、好ましくは多価アルコール等が挙げられる。該油状物質としては、通常医薬製剤中に用いられる可塑剤が挙げられ、具体的には、例えばクエン酸トリエチル、中鎖脂肪酸トリグリセリド、フタル酸ジエチル、フタル酸ジブチル、トリアセチン（トリアセチルグリセリン）、ブチルフタリルブチルグリコレート、グリセリルカプリル酸エステル等のエステル類；グリセリン、プロピレングリコール、ポリエチレングリコール等のアルコール類等が挙げられる。その他、ゴマ油、ヒマシ油等も油状物質として用いることができる。これらの油状物質は、１種または２種以上を適宜の割合で混合して用いてもよい。油状物質は、好ましくはアルコール類、より好ましくは多価アルコール、特に好ましくはポリエチレングリコールである。また、ポリエチレングリコールとしては、例えばポリエチレングリコール４００，ポリエチレングリコール６００，ポリエチレングリコール１５００，ポリエチレングリコール４０００，ポリエチレングリコール６０００などが挙げられる。油状物質の被覆剤中の含量は、例えば約０．１～約３０重量％、好ましくは約１０～約２０重量％である。上記油状物質を被覆剤に添加することにより、強度および展延性に優れ、操作性に優れた被覆剤を得ることができる。また、このような被覆剤を使用することにより、均一な被覆が可能となる。

【０００９】「塩基性物質」は、ギ酸などの酸を中和する塩基性を示す物質であればよく、具体的には、例えばアルカリ金属の炭酸水素塩（例、炭酸水素ナトリウム等）、アルカリ金属の炭酸塩（例、炭酸ナトリウム，炭酸カリウム等）、アルカリ土類金属の炭酸塩（例、炭酸カルシウム，炭酸マグネシウム等）などの金属の炭酸塩；アルカリ金属のリン酸水素二塩（例、リン酸水素二ナトリウム、リン酸水素二カリウム等）などのリン酸水素二塩；ケイ酸カルシウム、ケイ酸マグネシウムなどのケイ酸塩；酸化マグネシウムなどの金属酸化物；水酸化ナトリウム、水酸化カルシウム、水酸化マグネシウム、水酸化アルミニウムなどの金属水酸化物；クエン酸ナトリウムなどのクエン酸塩；ｄｌ－およびｌ－酒石酸ナトリウムなどの酒石酸塩；パントテン酸カルシウムなどのパントテン酸塩などの塩基性を示す塩、酸化物または水酸化物が挙げられる。これらの塩基性物質は、１種または２種以上を適宜の割合で混合して用いてもよい。塩基性物質は、好ましくは金属の炭酸塩または金属水酸化物であり、さらに好ましくは炭酸水素ナトリウム、炭酸ナトリウム、炭酸カリウム、炭酸カルシウム、炭酸マグネシウム、水酸化マグネシウムである。また、塩基性物質の被覆剤中の含量は、医薬製剤中で生ずるギ酸などの酸を中和するのに十分な量であればよく、例えば約０．１～約５０重量％、好ましくは約１～約２０重量％である。

【００１０】「被覆剤」は、上記した「紫外線によりフリーラジカルを発生しうる遮光剤」、「フリーラジカル消去剤」、「エステル類およびアルコール類から選ばれる油状物質」または「塩基性物質」の他に、コーティング基剤を含む。該コーティング基剤の被覆剤中の含量

は、一般製剤の製造に用いられる量である。また、「被覆剤」は、所望により、被覆剤および医薬製剤に悪影響を及ぼさない添加物をさらに含んでいてもよい。さらに、「被覆剤」は、上記各成分を水または有機溶媒に溶解または分散した液であってもよい。該有機溶媒の種類は、特に限定されず、例えばメタノール、エタノール、イソプロピルアルコール等のアルコール類；アセトン等のケトン類が使用できる。また、水と有機溶媒との混合液も使用することができる。

【００１１】上記コーティング基剤としては、例えば糖衣基剤、水溶性フィルムコーティング基剤、腸溶性フィルムコーティング基剤、徐放性フィルムコーティング基剤などが挙げられる。糖衣基剤としては、白糖が用いられ、さらに、タルク、沈降炭酸カルシウム、ゼラチン、アラビアゴム、プルラン、カルナバロウなどから選ばれる１種または２種以上を併用してもよい。水溶性フィルムコーティング基剤としては、例えばヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ヒドロキシエチルセルロース、メチルヒドロキシエチルセルロースなどのセルロース系高分子；ポリビニルアセタールジエチルアミノアセテート、アミノアルキルメタアクリレートコポリマーＥ〔オイドラギットＥ（商品名）、ロームファルマ社〕、ポリビニルピロリドンなどの合成高分子；プルランなどの多糖類などが挙げられる。腸溶性フィルムコーティング基剤としては、例えばヒドロキシプロピルメチルセルロース　フタレート、ヒドロキシプロピルメチルセルロース　アセテートサクシネート、カルボキシメチルエチルセルロース、酢酸フタル酸セルロースなどのセルロース系高分子；メタアクリル酸コポリマーＬ〔オイドラギットＬ（商品名）、ロームファルマ社〕、メタアクリル酸コポリマーＬＤ〔オイドラギットＬ－３０Ｄ５５（商品名）、ロームファルマ社〕、メタアクリル酸コポリマーＳ〔オイドラギットＳ（商品名）、ロームファルマ社〕などのアクリル酸系高分子；セラックなどの天然物などが挙げられる。徐放性フィルムコーティング基剤としては、例えばエチルセルロースなどのセルロース系高分子；アミノアルキルメタアクリレートコポリマーＲＳ〔オイドラギットＲＳ（商品名）、ロームファルマ社〕、アクリル酸エチル・メタアクリル酸メチル共重合体懸濁液〔オイドラギットＮＥ（商品名）、ロームファルマ社〕などのアクリル酸系高分子などが挙げられる。上記したコーティング基剤は、その２種以上を適宜の割合で混合して用いてもよい。

【００１２】上記した添加物としては、例えば着色剤、香料等が挙げられ、その添加量は、一般製剤の製造に用いられる量である。着色剤としては、例えば水溶性食用タール色素（例、食用赤色２号および３号、食用黄色４号および５号、食用青色１号および２号等）、水不溶性レーキ色素（前記水溶性食用タール色素のアルミニウム塩等）、天然色素（例、β－カロチン、クロロフィル等）などが挙げられる。香料としては、例えばレモン油、オレンジ、ｄｌ－またはｌ－メントールなどが挙げられる。

【００１３】本発明の「被覆剤」は、例えば上記した「紫外線によりフリーラジカルを発生しうる遮光剤」、「フリーラジカル消去剤」、「エステル類およびアルコール類から選ばれる油状物質」または「塩基性物質」などの各成分と、コーティング基剤とを、所望により上記添加物を添加した後、混合することにより製造される。また、「被覆剤」は、上記各成分を水または上記有機溶媒に溶解または分散することによっても製造され、このような製造方法により、均一な被覆を得ることができる。

【００１４】本発明の「医薬製剤」は、「薬物含有組成物」を上記被覆剤で被覆することにより得られる。該「薬物含有組成物」は、「薬物」単独であっても、「薬物」と医薬製剤の製造に用いられる慣用の「製剤成分」との混合物であってもよい。薬物含有組成物の剤形としては、例えば錠剤、散剤、顆粒剤、細粒剤および丸剤などが挙げられる。

【００１５】「薬物」としては、光、とりわけ紫外線により分解する薬物、フリーラジカルにより分解する薬物、フリーラジカルが製剤成分を分解して生じるアルデヒド類（例、ホルムアルデヒド、アセトアルデヒド），酸類（例、ギ酸）または過酸化物により分解する薬物などが挙げられる。このような薬物としては、例えば滋養強壮保健薬、解熱鎮痛消炎薬、向精神病薬、抗不安薬、抗うつ薬、催眠鎮静薬、鎮痙薬、中枢神経作用薬、脳代謝改善剤、抗てんかん剤、交感神経興奮剤、胃腸薬、制酸剤、抗潰瘍剤、鎮咳去痰剤、鎮吐剤、呼吸促進剤、気管支拡張剤、抗アレルギー薬、歯科口腔用薬、抗ヒスタミン剤、強心剤、不整脈用剤、利尿薬、血圧降下剤、血管収縮薬、冠血管拡張薬、末梢血管拡張薬、高脂血症治療剤、利胆剤、抗生物質、化学療法剤、糖尿病治療剤、骨粗しょう症治療剤、骨格筋弛緩薬、鎮うん剤、ホルモン剤、アルカロイド系麻薬、サルファ剤、痛風治療薬、血液凝固阻止剤、抗悪性腫瘍剤、アルツハイマー治療薬などから選ばれた１種または２種以上の成分が挙げられる。これら「薬物」の「医薬製剤」中の含量は、「薬物」の有効量であればよい。

【００１６】以下、上記した薬物の具体例を述べる。滋養強壮保健薬としては、例えばビタミンＡ、ビタミンＤ、ビタミンＥ（酢酸ｄ－α－トコフェロールなど）、ビタミンB_1（ジベンゾイルチアミン、フルスルチアミン塩酸塩など）、ビタミンB_2（酪酸リボフラビンなど）、ビタミンB_6（塩酸ピリドキシンなど）、ビタミンＣ（アスコルビン酸、Ｌ－アスコルビン酸ナトリウムなど）、ビタミンB_{12}（酢酸ヒドロキソコバラミンなど）のビタミン；カルシウム、マグネシウム、鉄などのミネラル；タンパク、アミノ酸、オリゴ糖、生薬などが

挙げられる。解熱鎮痛消炎薬としては、例えばアスピリン、アセトアミノフェン、エテンザミド、イブプロフェン、塩酸ジフェンヒドラミン、ｄｌ-マレイン酸クロルフェニラミン、リン酸ジヒドロコデイン、ノスカピン、塩酸メチルエフェドリン、塩酸フェニルプロパノールアミン、カフェイン、無水カフェイン、セラペプターゼ、塩化リゾチーム、トルフェナム酸、メフェナム酸、ジクロフェナクナトリウム、フルフェナム酸、サリチルアミド、アミノピリン、ケトプロフェン、インドメタシン、ブコロール、ペンタゾシンなどが挙げられる。向精神病薬としては、例えばクロルプロマジン、レセルピンなどが挙げられる。抗不安薬としては、例えばアルプラゾラム、クロルジアゼポキシド、ジアゼパムなどが挙げられる。抗うつ薬としては、例えばイミプラミン、マプロチリン、アンフェタミンなどが挙げられる。

【００１７】催眠鎮静薬としては、例えばエスタゾラム、ニトラゼパム、ジアゼパム、ペルラピン、フェノバルビタールナトリウムなどが挙げられる。鎮痙薬としては、例えば臭化水素酸スコポラミン、塩酸ジフェンヒドラミン、塩酸パパベリンなどが挙げられる。中枢神経作用薬としては、例えばシチコリン、ロチレニンなどが挙げられる。脳代謝改善剤としては、例えばイデベノン、ピンポセチン、塩酸メクロフェニキセート、８－〔１－オキソ－３－〔１－（フェニルメチル）ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピンまたはその塩などが挙げられる。抗てんかん剤としては、例えばフェニトイン、カルバマゼピンなどが挙げられる。交感神経興奮剤としては、例えば塩酸イソプロテレノールなどが挙げられる。胃腸薬としては、例えばジアスターゼ、含糖ペプシン、ロートエキス、セルラーゼＡＰ３、リパーゼＡＰ、ケイヒ油などの健胃消化剤；塩酸ベルベリン、耐性乳酸菌、ビフィズス菌などの整腸剤などが挙げられる。制酸剤としては、例えば炭酸マグネシウム、炭酸水素ナトリウム、メタケイ酸アルミン酸マグネシウム、合成ヒドロタルサイト、沈降炭酸カルシウム、酸化マグネシウムなどが挙げられる。抗潰瘍剤としては、例えばベンツイミダゾール系化合物（例、ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾール）、ファモチジン、シメチジン、塩酸ラニチジンなどが挙げられる。

【００１８】鎮咳去痰剤としては、例えば塩酸クロペラスチン、臭化水素酸デキストロメルトファン、テオフィリン、グァヤコールスルホン酸カリウム、グアイフェネシン、リン酸コデインなどが挙げられる。鎮吐剤としては、例えば塩酸ジフェニドール、メトクロプラミドなどが挙げられる。呼吸促進剤としては、例えば酒石酸レバロルファンなどが挙げられる。気管支拡張剤としては、例えばテオフィリン、硫酸サルブタノールなどが挙げられる。抗アレルギー薬としては、例えばアンレキサノクス、セラトロダストなどが挙げられる。歯科口腔用薬としては、例えばオキシテトラサイクリン、トリアムシノロンアセトニド、塩酸クロルヘキシジン、リドカインなどが挙げられる。抗ヒスタミン剤としては、例えば塩酸ジフェンヒドラミン、プロメタジン、塩酸イソチペンジル、ｄｌ-マレイン酸クロルフェニラミンなどが挙げられる。強心剤としては、例えばカフェイン、ジゴキシンなどが挙げられる。不整脈用剤としては、例えば塩酸プロカインアミド、塩酸プロプラノロール、ピンドロールなどが挙げられる。利尿薬としては、例えばイソソルビド、フロセミドなどが挙げられる。血圧降下剤としては、例えば塩酸デラプリル、カプトプリル、臭化ヘキサメトニウム、塩酸ヒドララジン、塩酸ラベタロール、塩酸マニジピン、カンデサルタン シレキセチル、メチルドーパ、ロサルタン、バルサルタン、エプロサルタン、イルベサルタン、タソサルタン、テルミサルタン、ポミサルタン、リピサルタン、フォラサルタンなどが挙げられる。

【００１９】血管収縮剤としては、例えば塩酸フェニレフリンなどが挙げられる。冠血管拡張剤としては、例えば塩酸カルボクロメン、モルシドミン、塩酸ベラパミルなどが挙げられる。末梢血管拡張薬としては、例えばシンナリジンなどが挙げられる。高脂血症治療剤としては、例えばセリバスタンチンナトリウム、シンバスタチン、プラバススタチンなどが挙げられる。利胆剤としては、例えばデヒドロコール酸、トレピプトンなどが挙げられる。抗生物質としては、例えばセファレキシン、アモキシシリン、塩酸ピブメシリナム、塩酸セフォチアム、塩酸セフォゾプラン、塩酸セフメノキシム、セフスロジンナトリウムなどのセフェム系抗生物質；アンピシリン、シクラシン、スルベニシリンナトリウム、ナリジクス酸、エノキサシンなどの合成抗菌剤；カルモナムナトリウムなどのモノバクタム系抗生物質；ペネム系抗生物質及びカルバペネム系抗生物質などが挙げられる。化学療法剤としては、例えば塩酸スルファメチゾール、チアゾスルホンなどが挙げられる。糖尿病治療剤としては、例えばトルブタミド、ボグリボース、チアゾリジンジオン誘導体（例、塩酸ピオグリタゾン、トログリタゾン、５－〔〔４－〔２－（メチル－２－ピリジニルアミノ）エトキシ〕フェニル〕メチル〕－２，４－チアゾリンジオン）、アカルボース、ミグリトール、エミグリテートなどが挙げられる。骨粗しょう症治療剤としては、例えばイプリフラボンなどが挙げられる。骨格筋弛緩薬としては、例えばメトカルバモールなどが挙げられる。鎮うん剤としては、例えば塩酸メクリジン、シメンヒドリナートなどが挙げられる。

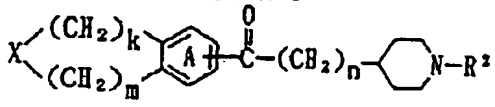
【００２０】ホルモン剤としては、例えばリオチニンナトリウム、リン酸デキメタゾンナトリウム、プレドニゾロン、オキセンドロン、酢酸リューブロレリンなどが挙げられる。アルカロイド系麻薬としては、例えばアヘン、塩酸モルヒネ、トコン、塩酸オキシコドン、塩酸ア

ヘンアルカロイド、塩酸コカインなどが挙げられる。サルファ剤としては、例えばスルファミン、スルファメチゾールなどが挙げられる。痛風治療薬としては、例えばアロプリノール、コルヒチンなどが挙げられる。血液凝固阻止剤としては、例えばジクマロールが挙げられる。抗悪性腫瘍剤としては、例えば５－フルオロウラシル、ウラシル、マイトマイシンなどが挙げられる。アルツハイマー病治療薬としては、例えばイデベノン、ビンポセチン、８－〔１－オキソ－３－〔１－（フェニルメチル）ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピンまたはその塩などが挙げられる。

【００２１】また、アミノ基またはイミノ基を有する「薬物」は、紫外線、フリーラジカル、またはフリーラジカルが製剤成分を分解して生じるアルデヒド類（例、ホルムアルデヒド、アセトアルデヒド），酸類（例、ギ酸）または過酸化物により分解しやすいので、「薬物」として、アミノ基またはイミノ基を有する「薬物」を用いることが好ましい。

【００２２】「薬物」は、さらに好ましくは式

【化１】



(I)

〔式中、XはR¹-N＜（R¹は水素原子、置換基を有していてもよい炭化水素基または置換基を有していてもよいアシル基を示す）、酸素原子または硫黄原子を示し、R²は水素原子または置換基を有していてもよい炭化水素基を示し、環Aは置換基を有していてもよいベンゼン環を、kは０～３の整数を、mは１～８の整数を、nは１～６の整数を示す。〕で表わされる化合物およびその塩である。前記式（Ｉ）において、R¹およびR²で示される「置換基を有していてもよい炭化水素基」の「炭化水素基」としては、例えば、鎖状、環状、飽和、不飽和、さらにはこれらの種々の組み合わせからなる炭化水素基が挙げられる。鎖状飽和炭化水素基としては、例えば、直鎖状もしくは分枝状の炭素数１～１１（C_{1-11}）のアルキル基（例えば，メチル，エチル，プロピル，イソプロピル，ブチル，イソブチル，tertーブチル，ペンチル，ヘキシル）が挙げられる。鎖状不飽和炭化水素基としては、直鎖状もしくは分枝状のC_{2-4}のアルケニル基（例えば、ビニル，アリル，２－ブテニル，イソプロペニル）およびC_{2-4}のアルキニル基（例、エチニル，２－プロピニル，２－ブチニル，３－ブチニル）が挙げられる。環状飽和炭化水素基としては、C_{3-7}の単環シクロアルキル基（例えば、シクロプロピル，シクロブチル，シクロペンチル，シクロヘキシル）およびC_{8-14}の架橋環式飽和炭化水素基（例えば、ビシクロ［３．２．１］オクト－２－イル，ビシクロ［３．３．１］ノン－２－イル，アダマンタン－1－イル）が挙げられる。環状不飽和炭化水素基としては、フェニル基、ナフチル基などが用いられる。

【００２３】また、前記の「炭化水素基」としては、先に例示した鎖状、環状、飽和、不飽和の炭化水素基の種々の組み合わせからなる炭化水素基でもよく、例えば、C_{7-18} アラルキル（例えば、トリル，キシリル；ベンジル，フェネチル，フェニルプロピル，フェニルブチル，フェニルペンチル，フェニルヘキシルなどのフェニル－C_{1-12} アルキル；α－ナフチルメチルなどのα－ナフチル－C_{1-8} アルキル），C_{8-18} アリールアルケニル（例えば、スチリル，シンナミル，４－フェニル－２－ブテニル，４－フェニル－３－ブテニルなどのフェニル－C_{2-12} アルケニル），C_{8-18} アリールアルキニル（例えば、フェネチル，３－フェニル－２－プロピニル，３－フェニル－１－プロピニルなどのフェニル－C_{2-12} アルキニル），C_{3-7} シクロアルキル－C_{1-6} アルキル（例えば、シクロプロピルメチル，シクロブチルメチル，シクロペンチルメチル，シクロヘキシルメチル，シクロヘプチルメチル，シクロプロピルエチル，シクロブチルエチル，シクロペンチルエチル，シクロヘキシルエチル，シクロヘプチルエチル，シクロプロピルブチル，シクロブチルブチル，シクロペンチルブチル，シクロヘキシルブチル，シクロヘプチルブチル，シクロプロピルペンチル，シクロブチルペンチル，シクロペンチルペンチル，シクロヘキシルペンチル，シクロヘプチルペンチル，シクロプロピルヘキシル，シクロブチルヘキシル，シクロペンチルヘキシル，シクロヘキシルヘキシル，シクロヘプチルヘキシル）等が挙げられる。

【００２４】R¹で表わされる「置換基を有していてもよい炭化水素基」の「炭化水素基」としては、上記の中でも直鎖状もしくは分枝状C_{1-7}アルキル基（例えば、メチル，エチル，プロピル，イソプロピル，ブチル，イソブチル，sec－ブチル，tertーブチル，ペンチル，イソペンチル，ヘキシル，ヘプチル）またはC_{7-10} アラルキル基（例えば、ベンジル，フェネチル，フェニルプロピル）などが好ましい。R²で表わされる「置換基を有していてもよい炭化水素基」の「炭化水素基」としては、上記の中でもC_{7-10} アラルキル（例えば、ベンジル，フェネチル，フェニルプロピル）などが好ましい。R¹，R²で表わされる上記の炭化水素は置換可能な位置に置換基を有していてもよい。R¹，R²で表わされる上記したような鎖状飽和、鎖状不飽和および環状飽和炭化水素基が有していてもよい置換基としては、例えばハロゲン原子（例えば、フッ素，塩素，臭素，ヨウ素）、ニ

トロ基、シアノ基、ヒドロキシ基、C_{1-4} アルコキシ基（例えば、メトキシ，エトキシ，プロピルオキシ，ブチルオキシ，イソプロピルオキシ）、C_{1-4} アルキルチオ基（例えば、メチルチオ，エチルチオ，プロピルチオ，イソプロピルチオ，ブチルチオ）、アミノ基、モノまたはジC_{1-4} アルキルアミノ基（例えば、メチルアミノ，エチルアミノ，プロピルアミノ，ジメチルアミノ，ジエチルアミノ）、環状アミノ基（例えば、ピロリジノ，ピペリジノ）、モルホリノ、C_{1-4} アルキルカルボニルアミノ基（例えば、アセチルアミノ，プロピオニルアミノ，ブチリルアミノ等のアルキル部分がC_{1-4} であるアルキルカルボニルアミノ）、C_{1-4} アルキルスルホニルアミノ基（例えば、メチルスルホニルアミノ，エチルスルホニルアミノ）、C_{1-4} アルコキシカルボニル基（例えば、メトキシカルボニル，エトキシカルボニル，プロポキシカルボニル）、ヒドロキシカルボニル基、C_{1-6} アルキルカルボニル基（例えば、アセチル，プロピオニル，ブチリル，バレリル，ヘプタノイル）、カルバモイル基、モノまたはジC_{1-4} アルキルカルバモイル基（例えば、Ｎ－メチルカルバモイル，Ｎ－エチルカルバモイル，Ｎ－プロピルカルバモイル，Ｎ－ブチルカルバモイル）、C_{1-6} アルキルスルホニル基（例えば、メチルスルホニル，エチルスルホニル，プロピルスルホニル）等が挙げられ、これらから選ばれた１ないし５個を有していてもよい。

【００２５】式（Ｉ）において環Ａで表わされる「置換基を有していてもよいベンゼン環」の置換基、R^1，R^2で表わされる環状不飽和炭化水素基の置換基としては、例えば、C_{1-4} アルキル基（例えば、メチル，エチル，プロピル，ブチル）、ハロゲン原子（例えば、フッ素，塩素，臭素，ヨウ素）、ニトロ基、シアノ基、ヒドロキシ基、C_{1-4} アルコキシ基（例えば、メトキシ，エトキシ，プロピルオキシ，ブチルオキシ，イソプロピルオキシ）、C_{1-4} アルキルチオ基（例えば、メチルチオ，エチルチオ，プロピルチオ，イソプロピルチオ，ブチルチオ）、アミノ基、モノまたはジC_{1-4} アルキルアミノ基（例えば、Ｎ－メチルアミノ，Ｎ－エチルアミノ，Ｎ－プロピルアミノ，Ｎ,Ｎ－ジメチルアミノ，Ｎ,Ｎ－ジエチルアミノ）、環状アミノ基（例えば、ピロリジノ，ピペリジノ）、モルホリノ、C_{1-4} アルキルカルボニルアミノ基（例えば、アセチルアミノ，プロピオニルアミノ，ブチリルアミノ）、アミノカルボニルオキシ基、モノまたはジC_{1-4} アルキルカルバモイルオキシ基（例えば、Ｎ－メチルカルバモイルオキシ，Ｎ－エチルカルバモイルオキシ，Ｎ,Ｎ－ジメチルカルバモイルオキシ，Ｎ,Ｎ－ジエチルカルバモイルオキシ）、C_{1-4} アルキルスルホニルアミノ基（例えば、メチルスルホニルアミノ、エチルスルホニルアミノ，プロピルスルホニルアミノ）、C_{1-4} アルコキシカルボニル基（例えばメトキシカルボニル，エトキシカルボニル，プロポキシカルボニル，イソプトキシカルボニル）、カルボキシ基、C_{1-6} アルキルカルボニル基（例えば、アセチル，プロピオニル，ブチリル，シクロヘキシルカルボニル）、カルバモイル基，モノまたはジC_{1-4} アルキルカルバモイル基（例えば、Ｎ－メチルカルバモイル，Ｎ－エチルカルバモイル，Ｎ－プロピルカルバモイル，Ｎ－ブチルカルバモイル，Ｎ,Ｎ－ジエチルカルバモイル，Ｎ,Ｎ－ジブチルカルバモイル）、C_{1-6} アルキルスルホニル基（例えば、メチルスルホニル，エチルスルホニル，プロピルスルホニル，シクロペンチルスルホニル，シクロヘキシルスルホニル）、１～４個の置換基を有していてもよいフェニル、ナフチル、フェノキシ、ベンゾイル、フェノキシカルボニル、フェニルC_{1-4} アルキルカルバモイル、フェニルカルバモイル、フェニルC_{1-4} アルキルカルボニルアミノ、ベンゾイルアミノ、フェニルC_{1-4} アルキルスルホニル、フェニルスルホニル、フェニルC_{1-4} アルキルスルフィニル、フェニルC_{1-4} アルキルスルホニルアミノまたはフェニルスルホニルアミノ基（それぞれのフェニル基またはナフチル基における置換基としては、例えば上記に例示したようなC_{1-4} アルキル基、C_{1-4} アルコキシ基、フッ素，塩素，臭素，ヨウ素などのハロゲン原子、水酸基、ベンジルオキシ基、アミノ基、モノまたはジC_{1-4} アルキルアミノ基、ニトロ基、C_{1-4} アルキルカルボニル基などが用いられる。）などが挙げられる。これら環Ａで表わされる「置換基を有していてもよいベンゼン環」または、R^1，R^2で表わされる環状不飽和炭化水素基の置換基の数は１～３個程度が適当である。

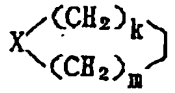
【００２６】R^1，R^2で表わされる「鎖状、環状、飽和、不飽和炭化水素基の種々の組み合わせからなる炭化水素基」の置換基としては、例えば、C_{1-4} アルキル基（例えば、メチル，エチル，プロピル，ブチル）、ハロゲン原子（例えば、フッ素，塩素，臭素，ヨウ素）、ニトロ基、シアノ基、ヒドロキシ基、C_{1-4} アルコキシ基（例えば、メトキシ，エトキシ，プロピルオキシ，ブチルオキシ，イソプロピルオキシ）、C_{1-4} アルキルチオ基（例えば、メチルチオ，エチルチオ，プロピルチオ，イソプロピルチオ，ブチルチオ）、アミノ基、モノまたはジC_{1-4} アルキルアミノ基（例えば、Ｎ－メチルアミノ，Ｎ－エチルアミノ，Ｎ－プロピルアミノ，Ｎ,Ｎ－ジメチルアミノ，Ｎ,Ｎ－ジエチルアミノ）、環状アミノ基（例えば、ピロリジノ，ピペリジノ）、モルホリノ、C_{1-4} アルキルカルボニルアミノ基（例えば、アセチルアミノ，プロピオニルアミノ，ブチリルアミノ）、カルバモイルオキシ基、モノまたはジC_{1-4} アルキルカルバモイルオキシ基（例えば、Ｎ－メチルカルバモイルオキシ，Ｎ－エチルカルバモイルオキシ，Ｎ,Ｎ－ジメチルカルバモイルオキシ，Ｎ,Ｎ－ジエチルカルバモイルオキシ）、C_{1-4} アルキルスルホニルアミノ基（例えば、メチルスルホニルアミノ、エチルスルホニルアミノ，プロピルスルホニルアミノ）、C_{1-4} アルコキシカルボニル基（例えばメトキシカルボニル，エトキシカルボニル，プ

ロポキシカルボニル，イソブトキシカルボニル)、ヒドロキシカルボニル基、C_{1-6} アルキルカルボニル基（例えば、アセチル，プロピオニル，ブチリル，シクロヘキシルカルボニル)、カルバモイル基、モノまたはジC_{1-4} アルキルカルバモイル基（例えば、Ｎ－メチルカルバモイル，Ｎ－エチルカルバモイル，Ｎ－プロピルカルバモイル，Ｎ－ブチルカルバモイル，Ｎ,Ｎ－ジエチルカルバモイル，Ｎ,Ｎ－ジブチルカルバモイル)、C_{1-6} アルキルスルホニル基（例えば、メチルスルホニル，エチルスルホニル，プロピルスルホニル，シクロペンチルスルホニル，シクロヘキシルスルホニル)、１～４個の置換基を有していてもよいフェニル、ナフチル、フェノキシ、ベンゾイル、フェノキシカルボニル、フェニルC_{1-4} アルキルカルバモイル、フェニルカルバモイル、フェニルC_{1-4} アルキルカルボニルアミノ、ベンゾイルアミノ、フェニルC_{1-4} アルキルスルホニル、フェニルスルホニル、フェニルC_{1-4} アルキルスルフィニル、フェニルC_{1-4} アルキルスルホニルアミノまたはフェニルスルホニルアミノ基（それぞれの環状基上の置換基としては、例えばメチル，エチル，プロピル，ブチル，イソプロピルなどのC_{1-4} アルキル基、メトキシ，エトキシ，プロピルオキシ，イソプロピルオキシ，ブチルオキシなどのC_{1-4} アルコキシ基、フッ素，塩素，臭素，ヨウ素などのハロゲン原子、水酸基、ベンジルオキシ基、アミノ基、上記のごときモノまたはジC_{1-4} アルキル置換アミノ基、ニトロ基、上記のごときC_{1-4} アルキルカルボニル基などが挙げられる。）などが挙げられる。これらの炭化水素基の置換の数は１～５個程度が適当である。

【００２７】R^1で示される「置換基を有していてもよいアシル基」の「アシル基」としては、カルボン酸アシル基（例えばホルミルや、アセチル，プロピオニル，ブチリル，ベンゾイルなどのC_{2-8} アルキルカルボニルまたはフェニルカルボニル)、スルホン酸アシル基（例えばメタンスルホニル，エタンスルホニル，プロパンスルホニル、ベンゼンスルホニル，ｐ－トルエンスルホニルなどのC_{1-7} アルキルスルホニルまたはフェニルスルホニル)、ホスホン酸アシル基（例えばメタンホスホニル，エタンホスホニル，プロパンホスホニル，ベンゼンホスホニルなどのC_{1-7} アルキルホスホニルまたはフェニルホスホニル)、置換オキシカルボニル基（例えば、エトキシカルボニル，tert－ブトキシカルボニル，ベンジルオキシカルボニルなどのC_{1-8} アルキルオキシカルボニル又はC_{7-8} アラルキルオキシカルボニル）が挙げられる。なかでも、C_{2-8} アルキルカルボニル基が好ましい。これらアシル基が有していてもよい置換基としては、ハロゲン原子（例えば、フッ素，塩素，臭素，ヨウ素)、アミノ基、C_{1-6} アルキル基（例えば、メチル，エチル，プロピル，ヘキシル）を有するモノ－またはジ－アルキルアミノ基、C_{1-4} アルコキシ基（例えば、メトキシ，エトキシ，プロポキシ）などが挙げられ、これらの基を置換可能な位置に１～３個好ましくは１～２個有していてもよい。

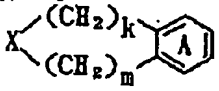
【００２８】式（Ｉ）で表される化合物（本明細書中、単に化合物（Ｉ）と略記することもある）の好ましい実施態様を以下に述べる。Ｘとしては、$R^1-N<$が好ましく、なかでもR^1が水素原子、直鎖状もしくは分枝状C_{1-3} アルキル基（例えば、メチル，エチル，プロピル，イソプロピル)、ベンジル、フェニル、C_{1-4} アルキルカルボニル（例えば、アセチル，プロピオニル，ブチリル)、ベンゾイル、C_{1-4} アルコキシカルボニル（例えば、メトキシカルボニル，エトキシカルボニル）などの場合がより好ましい。Ｘは、特に好ましくは$HN<$である。R^2としては、無置換あるいは１ないし２個のハロゲン原子（例えば、フッ素、塩素)、メチル、ニトロおよび/またはメトキシで置換されたベンジルまたはα－ナフチルメチル基が好ましく、特に無置換ベンジル基が好ましい。環Ａ上の置換基としては、フッ素、塩素、トリフルオロメチル、メチル、メトキシなどが好ましく、特にフッ素が好ましい。また、ｋとｍの和（ｋ＋ｍ）が２～６の整数のとき、すなわち

【化２】



が５～９員環を形成する場合が好ましく、なかでもｋ＋ｍが４の場合が好ましい。さらにｋ，ｍの組み合わせとしては、ｋが０のときｍとしては２，３，４または５が、ｋが１のときｍとしては１，２または３が、またｋが２のときはｍは２が好ましい。すなわち、

【化３】



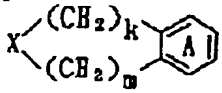
（$X=R^1-N<$）

で表される含窒素縮合複素環としては、２,３－ジヒドロ－１Ｈ－インドール、１,２,３,４－テトラヒドロキノリン、２,３,４,５－テトラヒドロ－１Ｈ－１－ベンズアゼピン、２,３－ジヒドロ－１Ｈ－イソインドール、１,２,３,４－テトラヒドロイソキノリン、２,３,４,５－テトラヒドロ－１Ｈ－２－ベンズアゼピン、２,３,４,５－テトラヒドロ－１Ｈ－３－ベンズアゼピン、１,２,３,４,５,６－ヘキサヒドロ－１－ベンズアゾシン、１,２,３,４,５,６－ヘキサヒドロ－２－ベンズアゾシン、１,２,３,４,５,６－ヘキサヒドロ－３－ベンズアゾシン、２,３,４,５,６,７－ヘキサヒドロ－１Ｈ－１－ベンズアゾニン、２,３,４,５,６,７－ヘキサヒドロ－１Ｈ－２－ベンズアゾニン、２,３,４,５,６,７－ヘキサヒドロ－１Ｈ－３－ベンズアゾニン、２,３,４,５,６,７－ヘキサヒドロ－１Ｈ－４－ベンズアゾニンが好ましい。

【００２９】

17

【化４】

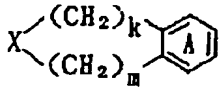


（X＝O）

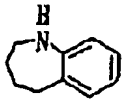
で表される含酸素縮合複素環としては、２，３－ジヒドロベンゾフラン、１，３－ジヒドロイソベンゾフラン、３，４－ジヒドロ－２Ｈ－１－ベンゾピラン、３，４－ジヒドロ－１Ｈ－２－ベンゾピラン、２，３，４，５－テトラヒドロ－１－ベンゾオキセピン、１，３，４，５－テトラヒドロ－２－ベンゾオキセピン、１，２，４，５－テトラヒドロ－３－ベンゾオキセピン、３，４，５，６－テトラヒドロ－２Ｈ－１－ベンゾオキソシン、３，４，５，６－テトラヒドロ－１Ｈ－２－ベンゾオキソシン、１，４，５，６－テトラヒドロ－２Ｈ－３－ベンゾオキソシン、２，３，４，５，６，７－ヘキサヒドロ－１－ベンゾオキソニン、１，３，４，５，６，７－ヘキサヒドロ－２－ベンゾオキソニン、１，２，４，５，６，７－ヘキサヒドロ－３－ベンゾオキソニン、１，２，３，５，６，７－ヘキサヒドロ－４－ベンゾオキソニンなどが好ましい。

【００３０】

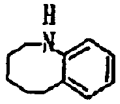
【化５】



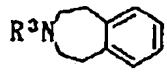
の好ましい縮合複素環としては、たとえば式



、



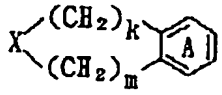
または



［式中、R^3は水素原子またはC_{1-3}アルキル基を示す。］で表わされる含窒素縮合複素環などであり、とりわけベンズアゼピン環が好ましい。上記式中、R^3で示されるC_{1-3}アルキル基はメチル，エチル，プロピル，イソプロピルである。ｎは、１、２または３、特に２が好ましい。化合物（Ｉ）は、特に好ましくは８－〔１－オキソ－３－〔１－（フェニルメチル）ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピンである。

【００３２】化合物（Ｉ）の塩としては、とりわけ生理学的に許容される酸付加塩が好ましい。それらの塩としては、例えば無機酸（例、塩酸、リン酸、臭化水素酸、硫酸）との塩、あるいは有機酸（例、酢酸、ギ酸、プロピオン酸、フマル酸、マレイン酸、コハク酸、酒石酸、クエン酸、リンゴ酸、蓚酸、安息香酸、メタンスルホン酸、ベンゼンスルホン酸）との塩等が挙げられる。さらに化合物（Ｉ）が、－ＣＯＯＨなどの酸性基を有している場合、化合物（Ｉ）は、無機塩基（例、ナトリウム、カリウム、カルシウム、マグネシウム、アンモニア）または有機塩基（例、トリエチルアミン）と塩を形成してもよい。化合物（Ｉ）の塩は、特に好ましくは有機酸塩

18



（X＝S）

で表される含硫黄縮合複素環としては、２，３－ジヒドロ［b］チオフェン、１，３－ジヒドロベンゾ［c］チオフェン、３，４－ジヒドロ－２Ｈ－１－ベンゾチオピラン、３，４－ジヒドロ－１Ｈ－２－ベンゾチオピラン、２，３，４，５－テトラヒドロ－１－ベンゾチエピン、１，３，４，５－テトラヒドロ－２－ベンゾチエピン、１，２，４，５－テトラヒドロ－３－ベンゾチエピン、３，４，５，６－テトラヒドロ－２Ｈ－１－ベンゾチオシン、３，４，５，６－テトラヒドロ－１Ｈ－２－ベンゾチオシン、１，４，５，６－テトラヒドロ－２Ｈ－３－ベンゾチオシン、２，３，４，５，６，７－ヘキサヒドロ－１－ベンゾチオニン、１，３，４，５，６，７－ヘキサヒドロ－２－ベンゾチオニン、１，２，４，５，６，７－ヘキサヒドロ－３－ベンゾチオニン、１，２，３，５，６，７－ヘキサヒドロ－４－ベンゾチオニンなどが好ましい。

【００３１】

【化６】

の好ましい縮合複素環としては、たとえば式

、

または

である。化合物（Ｉ）またはその塩は、特に好ましくは８－〔１－オキソ－３－〔１－（フェニルメチル）ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピン　フマレートである。化合物（Ｉ）またはその塩は、特開平５－１４０１４９号公報に記載の公知方法またはこれに準じる方法により製造されうる。

【００３３】上記した「製剤成分」としては、例えば賦形剤〔例、乳糖、白糖、Ｄ－マンニトール、Ｄ－ソルビトール、デンプン（トウモロコシデンプン、バレイショデンプンなど）、α化デンプン、デキストリン、結晶セルロース、低置換度ヒドロキシプロピルセルロース、カルボキシメチルセルロースナトリウム、アラビアゴム、デキストラン、プルラン、軽質無水ケイ酸、合成ケイ酸アルミニウム、メタケイ酸アルミン酸マグネシウムなど〕、結合剤（例、α化デンプン、ショ糖、ゼラチン、アラビアゴム粉末、メチルセルロース、カルボキシメチルセルロース、カルボキシメチルセルロースナトリウム、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、結晶セルロース、デキストリン、プルランなど）、滑沢剤（例、

ステアリン酸マグネシウム、ステアリン酸カルシウム、タルク、コロイドシリカなど）、崩壊剤〔例、乳糖、白糖、カルボキシメチルセルロース、低置換度ヒドロキシプロピルセルロース、デンプン（トウモロコシデンプン、バレイショデンプンなど）、軽質無水ケイ酸、クロスカルメロースナトリウム、カルボキシメチルスターチナトリウム、カルボキシメチルセルロースカルシウムなど〕、着色剤、香料、矯味剤、吸着剤、防腐剤、湿潤剤、帯電防止剤、崩壊延長剤等が挙げられる。上記した製剤成分の添加量は、一般製剤の製造に用いられる量を用いてもよい。

【００３４】本発明の「医薬製剤」の剤形としては、例えば錠剤、カプセル剤、散剤、顆粒剤、細粒剤、丸剤などが挙げられる。顆粒剤は、例えば粒径約５００～約１４１０μmの粒子を約９０重量%以上、粒径約１７７μm以下の粒子を約５重量%以下含有する。また、細粒剤は、例えば粒径約１０～約５００μmの粒子を約７５重量%以上、粒径約５００μm以上の粒子を約５重量%以下、粒径約１０μm以下の粒子を約１０重量%以下含有する。好ましい細粒剤は、粒径約１０５～約５００μmの粒子を約７５重量%以上、粒径約５００μm以上の粒子を約５重量%以下、粒径約７４μm以下の粒子を約１０重量%以下含有する。

【００３５】本発明の「医薬製剤」は、上記した「薬物」および「製剤成分」を常法により混合して得られる「薬物含有組成物」を「被覆剤」で被覆することにより製造される。被覆剤の使用量は、医薬製剤の剤形に応じて選択すればよい。医薬製剤に対する被覆剤（乾燥重量）の使用量は、例えば錠剤では約０．１～約３０重量%、好ましくは約０．５～約１０重量%程度であり；顆粒剤および丸剤では約０．１～約５０重量%、好ましくは約１～約２０重量%程度であり；細粒剤では約０．１～約１００重量%、好ましくは約１～約５０重量%程度である。

【００３６】被覆方法としては、自体公知の方法、例えばパンコーティング法、流動コーティング法、転動コーティング法さらにはそれらを組み合わせた方法などが採用できる。また、被覆剤が、水または有機溶媒を含む溶液または分散液である場合、被覆方法としてスプレーコーティング法も採用できる。被覆の際の温度は、通常約２５～約６０℃、好ましくは約２５～約４０℃である。また、被覆に要する時間は、被覆方法、被覆剤の特性や使用量、医薬製剤の特性などを考慮して適宜選択できる。

【００３７】本発明の「医薬製剤」は、例えば薬物として化合物（Ｉ）またはその塩を用いる場合、老年性痴呆、アルツハイマー病、ハンチントン舞踏病、運動過多病、躁病などの疾病の予防または治療に用いることができる。本発明の「医薬製剤」の投与量は、薬物の種類、対象疾患の種類、症状、剤形などを考慮して、薬物としての投与量が該薬物の有効量となるように選択すればよい。例えば薬物として化合物（Ｉ）またはその塩を用いる場合、「医薬製剤」は、化合物（Ｉ）またはその塩の投与量が、成人（体重６０ｋｇ）において一日あたり約０．０１mg～約１００mg、好ましくは約０．１～約３０mg、より好ましくは約０．３～約１０mgとなる範囲で、１回または２～３回に分けて投与される。

【００３８】以下、本発明の各種「医薬製剤」について具体的に述べる。「紫外線によりフリーラジカルを発生しうる遮光剤、およびフリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤」は、前述の「薬物含有組成物」を、「紫外線によりフリーラジカルを発生しうる遮光剤」および「フリーラジカル消去剤」を含有する被覆剤で被覆することにより製造される。該被覆剤は、さらにエステル類およびアルコール類から選ばれる油状物質を含有することが好ましい。この場合、被覆剤は、さらに塩基性物質を含有することが好ましい。また、該油状物質としては、ポリエチレングリコールが好ましい。該「医薬製剤」の好適な態様としては、「（ｉ）酸化チタンおよび（ｉｉ）亜硫酸水素ナトリウム，アスコルビン酸，アスコルビン酸ナトリウム，アスコルビン酸カルシウム，ｄｌ－α－トコフェロールまたは酢酸ｄｌ-α－トコフェロールを含有する被覆剤で被覆してなる安定化された医薬製剤」が挙げられる。また、「紫外線によりフリーラジカルを発生しうる遮光剤」および「フリーラジカル消去剤」を含有する被覆剤は、例えばこれらの成分をコーティング基剤とともに精製水に溶解または分散することにより製造される。

【００３９】「エステル類およびアルコール類から選ばれる油状物質、およびフリーラジカル消去剤を含有する被覆剤で被覆してなる安定化された医薬製剤」は、前述の「薬物含有組成物」を、「エステル類およびアルコール類から選ばれる油状物質」および「フリーラジカル消去剤」を含有する被覆剤で被覆することにより製造される。また、「エステル類およびアルコール類から選ばれる油状物質」および「フリーラジカル消去剤」を含有する被覆剤は、例えばこれらの成分をコーティング基剤とともに精製水に溶解または分散することにより製造される。

【００４０】「エステル類およびアルコール類から選ばれる油状物質、および塩基性物質を含有する被覆剤で被覆してなる安定化された医薬製剤」は、前述の「薬物含有組成物」を、「エステル類およびアルコール類から選ばれる油状物質」および「塩基性物質」を含有する被覆剤で被覆することにより製造される。該被覆剤は、さらに紫外線によりフリーラジカルを発生しうる遮光剤を含有することが好ましい。また、「エステル類およびアルコール類から選ばれる油状物質」および「塩基性物質」を含有する被覆剤は、例えばこれらの成分をコーティング基剤とともに精製水に溶解または分散することにより

製造される。

【００４１】

【発明の実施の形態】以下において、実施例および試験例により、本発明をより具体的に説明する。

【００４２】

【実施例】実施例１

精製水２３００ｇに、ヒドロキシプロピルメチルセルロース2910（ＴＣ－５）　１２９．６ｇおよびポリエチレングリコール6000　３０．０ｇを溶解し、酸化チタン２０．０ｇ、黄色三二酸化鉄０．４ｇおよび〔表１〕に示すフリーラジカル消去剤または塩基性物質（以下、これらを安定化剤と略記する）のそれぞれ１種２０．０ｇを分散させ、それぞれ被覆剤を製造した。

【表１】

安定化剤
フリーラジカル消去剤
亜硫酸水素ナトリウム
アスコルビン酸
d-α-トコフェロール
塩基性物質
炭酸水素ナトリウム

【００４３】実施例２

精製水２３００ｇに、ヒドロキシプロピルメチルセルロース2910（ＴＣ－５）　１２１．６ｇおよびポリエチレングリコール6000　３０．０ｇを溶解し、酸化チタン２０．０ｇ、黄色三二酸化鉄０．４ｇ、亜硫酸水素ナトリウム１４．０ｇおよび炭酸水素ナトリウム１４．０ｇを分散させ、被覆剤を製造する。

【００４４】実施例３

流動層造粒乾燥機（ＦＤ－３Ｓ、パウレック社）中で、８－〔１－オキソ－３－〔１－(フェニルメチル)ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピン　フマレート（以下、化合物Ａと略記する）４０．０ｇ、マンニトール１６００ｇおよびコーンスターチ２２０．０ｇを均一に混合後、機内で、ヒドロキシプロピルセルロース（ＨＰＣ－Ｌ）６０．０ｇを溶解した水溶液を噴霧して造粒し、ついで流動層造粒乾燥機中で乾燥した。得られる造粒物を、パワーミル粉砕機（Ｐ－３、昭和化学機械工作所）を用い、１．５㎜φパンチングスクリーンで解砕して整粒末とした。さらに、上記と同様の操作を繰り返して整粒末を得た。この整粒末を３４５６．０ｇとり、これにコーンスターチ１２６．０ｇとステアリン酸マグネシウム１８．０ｇを加え、タンブラー混合機（ＴＭ－１５、昭和化学機械工作所）で混合して打錠用顆粒とした。この顆粒をロータリー打錠機（コレクト１９Ｋ、菊水製作所）で６．５㎜φの杵を用いて重量１００．０㎎で打錠（打錠圧０．８トン／杵）し、裸錠とした。

【００４５】得られる裸錠に、フィルムコーティング機（ＨＣＴ－２０、フロイント産業）中で、実施例１で得られた各種被覆剤を噴霧し、１錠当たり化合物Ａを２．０㎎含有する、〔表２〕に示す処方のフィルムコーティング錠各２８００錠を得た。

【表２】

錠剤処方（１錠当たりの組成）：

組　成	配合量（㎎）
化合物Ａ	2.0
Ｄ－マンニトール	80.0
コーンスターチ	14.5
ヒドロキシプロピルセルロース	3.0
ステアリン酸マグネシウム	0.5
計（裸錠）	100.0
裸錠	100.0
（フィルム成分）	
ヒドロキシプロピルメチルセルロース2910	2.592
ポリエチレングリコール6000	0.6
酸化チタン	0.4
黄色三二酸化鉄	0.008
安定化剤	0.4
合　計	104.0

【００４６】実施例４

被覆剤として実施例２で製造した被覆剤を用いる以外は実施例３と同様にして、フィルムコーティング錠を製造する。

【００４７】比較例１

安定化剤を用いず、ヒドロキシプロピルメチルセルロー

ス2910（ＴＣ－５）の量を１錠当たり２．９９２mgとする以外は実施例３と同様にして、フィルムコーティング錠を製造した。

【００４８】試験例１

フィルムコーティング錠の安定性評価試験

実施例３および比較例１で得られたフィルムコーティング錠をプラスチックシャーレに入れ、シャーレの上面をポリ塩化ビニリデンフィルム（サランラップ、旭化成工業）で覆い、完全に密閉するためにシャーレの円周をセロハンテープで固定した。このシャーレに光照射〔光源：白色蛍光灯、照射量：１２０万ルクス・時間（１０００ルクス×５０日）〕した後、以下のような方法で、化合物Ａの分解生成物である１－メチル－８－〔１－オキソ－３－〔１－(フェニルメチル)ピペリジン－４－イル〕プロピル〕－２，３，４，５－テトラヒドロ－１Ｈ－１－ベンズアゼピン　フマレート（以下、分解物Ｉと略記する）およびポリエチレングリコールの分解生成物であるホルムアルデヒドの生成量を測定した。

〔分解物Ｉの定量方法〕化合物Ａが約２００μg／mlとなるように移動相で溶解し、非水系フィルター（０．４５μm）でろ過した後、次の条件で高速液体カラムクロマトグラフィー（ＨＰＬＣ）法により定量した。その生成量は、化合物Ａのイニシャル含量との比率で表した。

ＨＰＬＣ条件

検出器：紫外線吸光光度計、測定波長：２４５nm

カラム：ＴＳＫゲル－８０Ｔｓ、内径：４．６mm，長さ：１５０mm

カラム温度：４０℃

移動相：０．０５Ｍリン酸二水素カリウム溶液（ｐＨ３．０）－アセトニトリル混液（容積比＝２：１）

流量：１ml／分

保持時間：約２０分

〔ホルムアルデヒドの定量方法〕錠剤５錠を５０ml蒸留水に加え、３０分振盪して溶解し、４０００rpmで１０分間遠心分離する。上澄み液を水系フィルター（０．４５μm）でろ過して得られるろ液をホルムアルデヒド定量キット（ホルムアルデヒドーテストワコー、和光純薬工業）を用いて、比色定量（測定波長５５０nm）した。なお、分解物Ｉは、次のような物性を有している。

化学式：$C_{26}H_{34}N_2O$

分子量：３９０．２６７

【００４９】結果を〔表３〕に示す。表中、ＮＤは検出されなかったことを示す。化合物Ａの分解生成物である分解物Ｉの検出限界は０．０５％、ホルムアルデヒドの検出限界は４μg／錠である。

【表３】

	安定化剤	分解物Ｉの生成量（％）	ホルムアルデヒド量（μg／錠）
本発明	（実施例３）		
	亜硫酸水素ナトリウム	ND	6
	アスコルビン酸	ND	ND
	d-α-トコフェロール	ND	6
	炭酸水素ナトリウム	ND	２４
対照	（比較例１）		
	なし	５．３	１３１

〔表３〕に示されるように、安定化剤を用いることにより、分解物Ｉおよびホルムアルデヒドの生成が抑制された。すなわち、酸化チタン、ポリエチレングリコール6000および安定化剤を含有する被覆剤を用いることにより、該被覆剤で被覆された素錠中の化合物Ａの分解が抑制され、化合物Ａに悪影響を及ぼすホルムアルデヒドの生成量も抑制された。

【００５０】試験例２

塩基性物質またはフリーラジカル消去剤の化合物Ａに及ぼす影響の評価試験化合物Ａ、酸化チタン、ポリエチレングリコール6000、コーンスターチおよび安定化剤を、重量比が０．３：５：５：２．５：２．５となるように混合して粉末を得た。安定化剤としては、塩基性物質：炭酸水素ナトリウム、炭酸ナトリウム、炭酸カルシウム、炭酸マグネシウム、水酸化マグネシウムまたはフリーラジカル消去剤：d-α-トコフェロールを用いた。対照として、安定化剤をコーンスターチとする以外は上記と同様にして粉末を得た。得られる粉末をガラスシャーレに入れ、シャーレの上面をポリ塩化ビニリデンフィルム（サランラップ、旭化成工業）で覆い、完全に密閉するためにシャーレの円周をセロハンテープで固定した。このシャーレに光照射〔光源：ケミカルランプ、照射量：３５０μW／cm²×５日〕した後、試験例１と同様にして、分解物Ｉの生成量を測定した。

【００５１】結果を〔表４〕に示す。

【表４】

25　　26

	安定化剤	分解物Ｉの生成量（%）
本発明	塩基性物質	
	炭酸水素ナトリウム	０．０３
	炭酸ナトリウム	０．００
	炭酸カルシウム	０．００
	炭酸マグネシウム	０．００
	水酸化マグネシウム	０．００
	フリーラジカル消去剤	
	d-α－トコフェロール	０．００
対照	コーンスターチ	４．３９

〔表４〕に示されるように、化合物Ａ、酸化チタンおよびポリエチレングリコール6000を含有する粉末に、塩基性物質またはフリーラジカル消去剤を添加することにより、化合物Ａの分解が抑制された。

【００５２】

【発明の効果】本発明の医薬製剤は、光、とりわけ紫外線や熱に対して安定であり、保存安定性に優れる。また、該医薬製剤の表面が均一であるため、例えば刻印等の処理も容易であり、その仕上がりも美しい。さらに、該医薬製剤は、投与時に食道粘膜への癒着が見られない。本発明の被覆剤は、上記のように保存安定性に優れた医薬製剤を製造するための原料として有用である。また、該被覆剤は、強度および展延性に優れるため、操作性に優れ、均一な被覆が可能である。

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] To light (especially ultraviolet rays) or heat, this invention is stable and relates to the remedy pharmaceutical preparation excellent in preservation stability, and coating which is the raw material of such remedy pharmaceutical preparation.
[0002]
[Description of the Prior Art] When formaldehyde (the thing contained as an impurity of a polyethylene glycol 400 and the thing to produce according to air oxidation of a polyethylene glycol 400 are included) and an O6-benzyl guanine react, it is known that an O6-benzyl guanine will decompose in polyethylene-glycol 400 water solution and under a room temperature [the Pharma shoe CHIKARU research (Pharmaceutical Research), 11 volumes, No. 7, 1060 - 1064 pages, and 1994]. Performing enteric coating using the enteric film liquid containing titanium oxide and a polyethylene glycol 6000 is indicated by JP,63-301816,A (EP disclosure No. 0277741). Vitamin C, an in KYO (Yinqiao) extract, acetaminophen, Chlorpheniramine, a calcium carbonate, starch, a dextran, peppermint oil, The tablet which has the volatile oil of in KYO (Yinqiao) and a gin fan (jingfang) The hydroxypropyl methylcellulose, No2 The tablet covered with the component containing enteric vinyl resin, PEG6000, sesame oil, Tween 80, talc, titanium oxide, magnesium stearate, a hood color, 95% ethanol, and distilled water is chemical. The abs truck shoes It is indicated by 122:238853. JP,63-166824,A -- light -- the elastic capsule covered with the coating in which at least 85% contains the particle titanium oxide not more than particle diameter 0.1micrometer in the unstable drug content oleaginous solution is indicated.
[0003]
[Problem(s) to be Solved by the Invention] When providing a consumer with unstable remedy pharmaceutical preparation to light, it is necessary to perform a protection-from-light package or protection-from-light coat of remedy pharmaceutical preparation. However, if the state of preservation of the chemist's shop in a hospital or the remedy pharmaceutical preparation by the side of a patient is taken into consideration, it will be hard to say that the quality of remedy pharmaceutical preparation can be enough guaranteed by protection-from-light package. Therefore, when manufacturing unstable remedy pharmaceutical preparation to light, to perform a protection-from-light coat is desired. However, when coating which contains protection-from-light agents, such as titanium oxide, and plasticizers, such as a polyethylene glycol, on the occasion of pharmaceutical-preparation-izing of an unstable drug to light was covered to the drug content tablet, the trouble that the film coated tablet obtained was inferior to the tablet before performing coat processing in the stability over light became clear.
[0004]
[Means for Solving the Problem] When stabilization of the drug in the inside of a film coated tablet was considered in view of such a trouble, it found out that the titanium oxide in coating generates a free radical by 1 ultraviolet rays, that alcohols, such as a drug and a polyethylene glycol in coating, decompose with two free radicals, and that acids, such as aldehydes, such as the decomposition product of alcohols, such as a polyethylene glycol, for example, formaldehyde, and an acetaldehyde, and a formic acid, and a peroxide caused disassembly of a drug further in 3

coating. Based on such knowledge, the drug destabilization factor was canceled further, and this invention was completed, as a result of inquiring in order to obtain the remedy pharmaceutical preparation with which versatility was stabilized. That is, this invention is stable remedy pharmaceutical preparation which it comes to cover with the protection-from-light agent which may generate a free radical by (1) and (i) ultraviolet rays, and coating containing (ii) free radical elimination agent.;
(2) Remedy pharmaceutical preparation of the above-mentioned (1) publication with which coating comes to contain the oil further chosen from ester and alcohols;
(3) Remedy pharmaceutical preparation of the above-mentioned (1) publication whose protection-from-light agent which may generate a free radical by ultraviolet rays is a metallic oxide;
(4) Remedy pharmaceutical preparation of the above-mentioned (3) publication whose metallic oxide is titanium oxide, an iron sesquioxide, or a zinc oxide;
(5) Remedy pharmaceutical preparation of the above-mentioned (1) publication whose free radical elimination agent is a sulfite or vitamins;
(6) Vitamins are vitamin C or remedy pharmaceutical preparation given in vitamin-E above-mentioned [a certain] (5).;
(7) Remedy pharmaceutical preparation of the above-mentioned (2) publication whose oil is a polyethylene glycol;
(8) Stable remedy pharmaceutical preparation which it comes to cover with coating containing (i) titanium oxide and the (ii) sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol;
(9) Remedy pharmaceutical preparation of the above-mentioned (2) publication with which coating contains an alkali further;
(10) Remedy pharmaceutical preparation of the above-mentioned (9) publication whose alkali is a metaled carbonate or a metaled metal hydroxide.
(11) The oil chosen from (i) ester and alcohols, and stable remedy pharmaceutical preparation which it comes to cover with coating containing (ii) free radical elimination agent;
(12) The oil chosen from (i) ester and alcohols, and stable remedy pharmaceutical preparation which it comes to cover with coating containing the (ii) alkali;
(13) Remedy pharmaceutical preparation of the above (12) with which coating comes to contain the protection-from-light agent which may generate a free radical by ultraviolet rays further;
(14) The protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating characterized by containing (ii) free radical elimination agent;
(15) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with the protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating containing (ii) free radical elimination agent;
(16) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with the oil chosen from (i) ester and alcohols, and coating containing (ii) free radical elimination agent;
(17) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with coating containing the oil chosen from (i) ester and alcohols, and the (ii) alkali;
(18) Activity for remedy pharmaceutical preparation stabilization of the protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating containing (ii) free radical elimination agent;
(19) It is related with the activity for remedy pharmaceutical preparation stabilization of coating containing the oil chosen from activity;, (20) (i) ester, and alcohols for remedy pharmaceutical preparation stabilization of the oil chosen from (i) ester and alcohols, and coating containing (ii) free radical elimination agent, and the (ii) alkali.
[0005] "The protection-from-light agent which may generate a free radical by ultraviolet rays" used for below in this invention, a "free radical elimination agent", "the oil chosen from ester and alcohols", a "alkali", "coating", and "remedy pharmaceutical preparation" are explained in full detail.

[0006] "The protection-from-light agent which may generate a free radical by ultraviolet rays" means what is added in remedy pharmaceutical preparation for the purpose of protection from light, and may generate a free radical by ultraviolet rays. Generally, these protection-from-light agent is ordinary temperature, and means what generates a free radical by exposing to the bottom of an indoor fluorescent lamp or outdoor daylight. As a free radical, O2, -, etc. are mentioned, for example. As such a protection-from-light agent, the oxide of inorganic substances, such as titanium oxide, an iron sesquioxide, and a zinc oxide, is mentioned, for example. A protection-from-light agent is a metallic oxide preferably, and titanium oxide still more preferably. Moreover, when using titanium oxide, the particle diameter is usually about 0.1 - 0.7 micrometers of abbreviation preferably about 0.01 - 1.5 micrometers of abbreviation. The contents in coating of "the protection-from-light agent which may generate a free radical by ultraviolet rays" are [that what is necessary is just the amount which can attain the object of protection from light of remedy pharmaceutical preparation] about 10 - 30 % of the weight of abbreviation preferably about 5 - 30 % of the weight of abbreviation.
[0007] A "free radical elimination agent" should just be matter which controls decomposition of the matter which can eliminate the above mentioned free radical and the coating component by oxidation reaction, or a remedy pharmaceutical preparation component. As a free radical elimination agent, for example Organic-acid; tryptophans [, such as an sugar-alcohol; benzoic acid], such as a mannitol, amino acid [, such as a cysteine,]; -- carbonate ion; -- metal complex; sodium hydrogensulfites, such as a copper complex and a manganese complex, -- Sulfites, such as a sodium sulfite and sodium metabisulfite; Sodium formaldehyde sulfoxylate (Rongalite), thiol derivative [, such as thioglycerol,]; -- natural resin [, such as guaiac resin,]; -- nordihydroguaiaretic acid -- Phenol derivatives, such as propyl gallate, burylhydroxyanisole, and dibutylhydroxytoluene; Erythorbic acid, sodium erythorbate and vitamin C (ascorbic acid ester, such as an example, ascorbyl palmitate, ascorbic-acid dipalmitate, and ascorbic-acid stearate, --) Ascorbic-acid salts, such as sodium ascorbate and calcium ascorbate, vitamin E (an example, the succinic-acid dl-alpha-tocopherol, the succinic-acid d-alpha-tocopherol, succinic-acid dl-alpha-tocopherol calcium, the acetic-acid dl-alpha-tocopherol, and the acetic-acid d-alpha-tocopherol --) The ester of tocopherols, such as nicotinic-acid dl-alpha-tocopherol Peptides [, such as a vitamin; glutathione], such as dl-alpha-tocopherol, d-alpha-tocopherol, a dl-delta-tocopherol, a d-delta-tocopherol, natural vitamin E, and beta carotene; pudding derivatives, such as a uric acid, etc. are mentioned. Two or more sorts may be mixed and used for these free radical elimination agents at one sort or a proper rate. A "free radical elimination agent" is a sulfite or vitamins (especially vitamin C and vitamin E) preferably, and is a sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol still more preferably. Moreover, in order to reinforce an operation of a "free radical elimination agent", ethylenediaminetetraacetic acid or its salt may be used together. The content in coating of a "free radical elimination agent" should just be an amount which can eliminate the free radical generated from the "protection-from-light agent which may generate a free radical by ultraviolet rays" contained in coating. The contents in coating of a "free radical elimination agent" are about 1 - 20 % of the weight of abbreviation preferably about 0.1 - 50 % of the weight of abbreviation.
[0008] as "the oil chosen from ester and alcohols" -- about 20- about 65 degrees C -- oil-like ester and alcohols -- polyhydric alcohol etc. is mentioned preferably. As this oil, the plasticizer usually used into remedy pharmaceutical preparation is mentioned, and, specifically, alcohols, such as ester; glycerols, such as citric-acid triethyl, a medium-chain-fatty-acid triglyceride, a diethyl phthalate, dibutyl phtalate, a triacetin (thoria cetyl glycerol), butyl phthalyl butyl glycolate, and glyceryl caprylic-acid ester, propylene glycol, and a polyethylene glycol, etc. are mentioned. In addition, sesame oil, castor oil, etc. can be used as oil. These oil may mix two or more sorts at one sort or a proper rate, and may be used. oil -- desirable -- alcohols -- more -- desirable -- polyhydric alcohol -- it is a polyethylene glycol especially preferably. Moreover, as a polyethylene glycol, a polyethylene glycol 400, a polyethylene glycol 600, a polyethylene glycol 1500, a polyethylene glycol 4000, a polyethylene glycol 6000, etc. are mentioned, for example. The contents in coating of oil are about 10 - 20 % of the weight of abbreviation preferably about

0.1 - 30 % of the weight of abbreviation. By adding the above-mentioned oil to coating, coating which was excellent in reinforcement and plasticity and was excellent in operability can be obtained. Moreover, a uniform coat is attained by using such coating.

[0009] That a "alkali" should just be matter in which the basicity which neutralizes acids, such as a formic acid, is shown specifically for example, the hydrogencarbonates (an example, sodium hydrogencarbonate, etc.) of alkali metal and the carbonate (an example --) of alkali metal the carbonate (an example --) of alkaline earth metal, such as a sodium carbonate and potassium carbonate a calcium carbonate, a magnesium carbonate, etc. -- etc. -- phosphoric-acid hydrogen 2 metaled salt (an example --) of carbonate; alkali metal disodium hydrogenphosphate, the potassium phosphate, etc. -- etc. -- phosphoric-acid hydrogen 2 -- a salt; calcium silicate -- silicates [, such as a magnesium silicate,]; -- metallic-oxides [, such as a magnesium oxide,]; -- a sodium hydroxide -- Tartrates, such as citrate;dl- [, such as a metal hydroxide; sodium citrate,], such as a calcium hydroxide, a magnesium hydroxide, and an aluminum hydroxide, and l-sodium tartrate; The salt which shows basicity, such as pantothenic acid salts, such as calcium pantothenate, An oxide or a hydroxide is mentioned. Two or more sorts may be mixed and used for these alkalis at one sort or a proper rate. An alkali is a metaled carbonate or a metaled metal hydroxide preferably, and are a sodium hydrogencarbonate, a sodium carbonate, potassium carbonate, a calcium carbonate, a magnesium carbonate, and a magnesium hydroxide still more preferably. Moreover, the contents in coating of an alkali are [that what is necessary is just sufficient amount to neutralize acids, such as a formic acid produced in remedy pharmaceutical preparation,] about 1 - 20 % of the weight of abbreviation preferably about 0.1 - 50 % of the weight of abbreviation.

[0010] "Coating" contains the coating basis other than the above-mentioned "protection-from-light agent which may generate a free radical by ultraviolet rays", a "free radical elimination agent", "the oil chosen from ester and alcohols", or a "alkali." The content in coating of this coating basis is an amount used for manufacture of common pharmaceutical preparation. Moreover, "coating" may contain further the additive which does not have an adverse effect on coating and remedy pharmaceutical preparation by request. Furthermore, "coating" may be the liquid which dissolved or distributed each above-mentioned component to water or an organic solvent. Especially the class of this organic solvent is not limited, for example, ketones [, such as an alcohols; acetone,], such as a methanol, ethanol, and isopropyl alcohol, can be used for it. Moreover, the mixed liquor of water and an organic solvent can also be used.

[0011] As the above-mentioned coating basis, a glycocalyx basis, a water-soluble film coating basis, an enteric film coating basis, a sustained-release film coating basis, etc. are mentioned, for example. As a glycocalyx basis, white soft sugar is used and one sort chosen from talc, a precipitated calcium carbonate, gelatin, gum arabic, a pullulan, a cull navarho, etc. or two sorts or more may be further used together. as a water-soluble film coating basis, polysaccharide [, such as a synthetic macromolecule; pullulan], such as cellulose type giant-molecule; polyvinyl-acetal diethylamino acetate, such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, and methyl hydroxyethyl cellulose, aminoalkylmetaacrylatecopolymer E [OIDORAGITTOE (trade name) and loam FARUMA], and a polyvinyl pyrrolidone, etc. is mentioned, for example. As an enteric film coating basis, it is the hydroxypropyl methylcellulose, for example. Phthalate, Hydroxypropyl methylcellulose Acetate succinate, Cellulose type macromolecules, such as carboxy methyl ethyl cellulose and cellulose acetate phthalate; Methacrylic acid copolymer L[OIDORAGITTOL (trade name) Loam FARUMA], methacrylic acid copolymer LD[OIDORAGITTO L-30D55 (trade name), Acrylic-acid system macromolecules, such as loam FARUMA] and methacrylic acid copolymer S [OIDORAGITTOS (trade name) and loam FARUMA]; natural products, such as a shellac, etc. are mentioned. As a sustained-release film coating basis, acrylic-acid system macromolecules, such as OIDORAGITTO RS (trade name) and cellulose type macromolecule [, such as ethyl cellulose,]; aminoalkylmetaacrylatecopolymer RS [loam FARUMA] ethyl-acrylate methacrylic acid methyl copolymer suspension [OIDORAGITTO NE (trade name) and loam FARUMA], etc. are mentioned, for example. Two or more sorts may be mixed and used for the above-mentioned coating basis at the proper rate.

[0012] As the above-mentioned additive, a coloring agent, perfume, etc. are mentioned, for

example and the addition is an amount used for manufacture of common pharmaceutical preparation. As a coloring agent, water-soluble edible tar dyes (an example, Food Red No.2 and No. 3, Food Yellow No.4 and No. 5, Food Blue No.1, No. 2, etc.), water-insoluble nature lake coloring matter (aluminum salt of said water-soluble edible tar dyes etc.), natural coloring matter (an example, beta carotene, chlorophyll, etc.), etc. are mentioned, for example. As perfume, lemon oil, Orange, dl-, or l-menthol is mentioned, for example.

[0013] "Coating" of this invention is manufactured by mixing, after adding the above-mentioned additive for each component, such as the above-mentioned "protection-from-light agent which may generate a free radical by ultraviolet rays", a "free radical elimination agent", "oil chosen from ester and alcohols", or a "alkali", and a coating basis by request. Moreover, "coating" is manufactured also by dissolving or distributing each above-mentioned component to water or the above-mentioned organic solvent, and can obtain a uniform coat by such manufacture approach.

[0014] The "remedy pharmaceutical preparation" of this invention is obtained by covering a "drug content constituent" with the above-mentioned coating. Even if ** "a drug content constituent" is "drug" independent, they may be a "drug" and mixture with the "pharmaceutical preparation component" of common use used for manufacture of remedy pharmaceutical preparation. As dosage forms of a drug content constituent, a tablet, powder, a granule, a fine grain agent, a pill, etc. are mentioned, for example.

[0015] The drug disassembled as a "drug" with light, the drug especially disassembled by ultraviolet rays, the drug disassembled with a free radical, the aldehydes (an example, formaldehyde, acetaldehyde) which a free radical decomposes a pharmaceutical preparation component and produces, acids (an example, formic acid), or a peroxide is mentioned. As such a drug, for example A nourishment strong preservative, an alleviation-of-fever painkilling antiphlogistic, A psychopharmaceutical, an anti-anxiety drug, an antidepressant, a sedative hypnotic, antispasmodic, a central nervous system acting drug, A brain metabolism improvement agent, an antiepiletic agent, a sympathomimetic drug, digestive medicine, antacid, antiulcer drug, Expectorant cough suppressant, antemetic, a respiratory accelerator, a bronchodilator, an antiallergic drug, An agent for dental and oral use, an antihistamine, cardiotonic, the agent for arrhythmia, diuretic, an antihypertensive, A vasoconstrictor, a coronary vasodilator, a peripheral vasodilator, antilipemic, a choleretic drug, One sort or two sorts or more of components chosen from an antibiotic, a chemotherapic drug, a diabetes-mellitus therapy agent, an osteoporosis therapy agent, a neuromuscular junction blocking drug, a ****** agent, a hormone drug, alkaloid system narcotics, sulfa drugs, the arthrifuge, the anticoagulant, the anticancer drug, the Alzheimer remedy, etc. are mentioned. The content in the "remedy pharmaceutical preparation" of these "a drug" should just be an effective dose of a "drug."

[0016] Hereafter, the example of the above-mentioned drug is described. As a nourishment strong preservative, mineral; proteins, such as vitamin A, vitamin D, vitamin E (acetic-acid d-alpha-tocopherol etc.), vitamins B1 (dibenzoyl thiamine, fursultiamine hydrochloride, etc.), vitamins B2 (riboflavin tetrabutyrate etc.), vitamins B6 (pyridoxine hydrochloride etc.), vitamin C, vitamin; calcium (an ascorbic acid, sodium L-ascorbate, etc.) of vitamins B12 (hydroxocobalamin acetate etc.), magnesium, and iron, amino acid, an oligosaccharide, a crude drug, etc. are mentioned, for example. As an alleviation-of-fever painkilling antiphlogistic, aspirin, acetaminophen, ethenzamide, ibuprofen, diphenhydramine hydrochloride, dl-chlorpheniramine maleate, dihydrocodeine phosphate, NOSUKABIN, methylephedrine hydrochloride, the phenylpropanolamine hydrochloride, caffeine, anhydrous caffeine, serrapeptase, lysozyme chloride, tolfenamic acid, mefenamic acid, diclofenac sodium, flufenamic acid, salicylamide, aminopyrine, ketoprofen, indomethacin, BUKORORU, pentazocine, etc. are mentioned, for example. As a psychopharmaceutical, chlorpromazine, reserpine, etc. are mentioned, for example. As an anti-anxiety drug, alprazolam, chlordiazepoxide, diazepam, etc. are mentioned, for example. As an antidepressant, imipramine, maprotiline, an amphetamine, etc. are mentioned, for example.

[0017] As a sedative hypnotic, estazolam, nitrazepam, diazepam, the perlapine, phenobarbital sodium, etc. are mentioned, for example. As antispasmodic, scopolamine hydrobromide, diphenhydramine hydrochloride, papaverine hydrochloride, etc. are mentioned, for example. As a

central nervous system acting drug, citicoline, ROCHIRENIN, etc. are mentioned, for example. As a brain metabolism improvement agent, IDEBENON, vinpocetine, hydrochloric-acid MEKUROFENIKISETO, 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine or its salt is mentioned, for example. As an antiepiletic agent, phenytoin, carbamazepine, etc. are mentioned, for example. As a sympathomimetic drug, isoproterenol hydrochloride etc. is mentioned, for example. As digestive medicine, medicines for intestinal disorders, such as stomachic digestive; hydrochloric-acid pel PERIN, such as diastase, saccharated pepsin, an extract of scopolia, cellulase AP 3, lipase AP, and cinnamon oil, antibiotics-resistant lactic acid bacteriae, and lactobacillus bifidus, etc. are mentioned, for example. As antacid, a magnesium carbonate, a sodium hydrogencarbonate, magnesium aluminometasilicate, synthetic hydrotalcite, a precipitated calcium carbonate, a magnesium oxide, etc. are mentioned, for example. As antiulcer drug, the Benz imidazole system compound (an example, lansoprazole, omeprazole, rabeprazole, punt PURAZORU), famotidine, cimetidine, ranitidine hydrochloride, etc. are mentioned, for example.

[0018] As expectorant cough suppressant, hydrochloric-acid cloperastine, a hydrobromic-acid DEKISUTORO melt fan, theophylline, a GUAYA call sulfonic-acid potassium, guaifenesin, codein phosphate, etc. are mentioned, for example. As antemetic, difenidol hydrochloride, metoclopramide, etc. are mentioned, for example. As a respiratory accelerator, levallorphan tartrate etc. is mentioned, for example. As a bronchodilator, theophylline, a sulfuric-acid ape butanol, etc. are mentioned, for example. As an antiallergic drug, amlexanox, seratrodast, etc. are mentioned, for example. As an agent for dental and oral use, oxytetracycline, triamcinolone acetonide, chlorhexidine hydrochloride, lidocaine, etc. are mentioned, for example. As an antihistamine, diphenhydramine hydrochloride, a promethazine, isothipendyl hydrochloride, dl-chlorpheniramine maleate, etc. are mentioned, for example. As cardiotonic, caffeine, digoxin, etc. are mentioned, for example. As an agent for arrhythmia, procainamide hydrochloride, propranolol hydrochloride, pindolol, etc. are mentioned, for example. As diuretic, iso SORUPIDO, furosemide, etc. are mentioned, for example. As an antihypertensive, they are delapril hydrochloride, captopril, a hexamethonium bromide, hydralazine hydrochloride, a hydrochloric-acid RAPETA roll, manidipine hydrochloride, and candesartan, for example. SHIREKI cetyl, methyldopa, a Losartan, valsartan, EPURO sultan, irbesartan, tasosartan, telmisartan, POMISARUTAN, RIPISARUTAN, FORA sultan, etc. are mentioned.

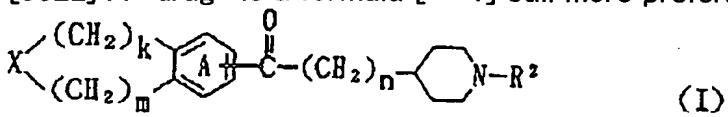
[0019] As vasoconstrictor, phenylephrine hydrochloride etc. is mentioned, for example. As a coronary vasodilator, carbocromen hydrochloride, molsidomine, hydrochloric-acid PERAPAMIRU, etc. are mentioned, for example. As a peripheral vasodilator, cinnarizine etc. is mentioned, for example. As antilipemic, auction bus TANCHIN sodium, simvastatin, PURABASUSUTACHIN, etc. are mentioned, for example. As a choleretic drug, dehydrocholic acid, TOREPIPUTON, etc. are mentioned, for example. As an antibiotic, monobactam antibiotic; penem system antibiotics [, such as synthetic-antimicrobials; carumonam sodium,], such as cephem antibiotic; ampicillins, such as cefalexin, amoxicillin, hydrochloric-acid PIPUMESHIRINAMU, cefotiam dihydrochloride, cefozopran hydrochloride, cefmenoxime hydrochloride, and cefsulodin sodium, SHIKURASHIN, sulbenicillin sodium, nalidixic acid, and enoxacin, a KARUPA penem system antibiotic, etc. are mentioned, for example. As a chemotherapic drug, hydrochloric-acid sulfamethizole, thiazosulfone, etc. are mentioned, for example. As a diabetes-mellitus therapy agent, tolbutamide, voglibose, a thiazolidinedione derivative (an example, pioglitazone hydrochloride, troglitazone, 5-[[4-[2-(methyl-2-pilus JINIRU amino) ethoxy] phenyl] methyl]-2, 4-thiazoline dione), acarbose, a MIGURI toll, EMIGURITETO, etc. are mentioned, for example. As an osteoporosis therapy agent, ipriflavone etc. is mentioned, for example. As a neuromuscular junction blocking drug, a METOKARUPA mall etc. is mentioned, for example. As a ****** agent, the meclizine hydrochloride, cymene HIDORINATO, etc. are mentioned, for example.

[0020] As a hormone drug, RIOCHININ sodium, phosphoric-acid DEKIMETAZON sodium, prednisolone, oxendolone, leuprorelin acetate, etc. are mentioned, for example. As alkaloid system narcotics, opium, morphine hydrochloride, ipecac, oxycodone hydrochloride, opium alkaloids hydrochlorides, cocaine hydrochloride, etc. are mentioned, for example. As sulfa drugs, sulfamine, sulfamethizole, etc. are mentioned, for example. As arthrifuge, allopurinol, a colchicine,

etc. are mentioned, for example. As an anticoagulant, dicumarol is mentioned, for example. As an anticancer drug, 5-fluorouracil, a uracil, a mitomycin, etc. are mentioned, for example. As an Alzheimer disease remedy, IDEBENON, vinpocetine, 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine or its salt is mentioned, for example.

[0021] Moreover, since the aldehydes (the example, the formaldehyde, acetaldehyde), the acids (the example, formic acid), or the peroxide which ultraviolet rays, a free radical, or a free radical decomposes a pharmaceutical preparation component, and produces is easy to decompose, as for the "drug" which has an amino group or an imino group, it is desirable to use as a "drug" the "drug" which has an amino group or an imino group.

[0022] A "drug" is a formula [** 1] still more preferably.



(I)

the inside of [type, and X -- R1-N -- < (R1 shows the acyl group which may have the hydrocarbon group which may have the hydrogen atom and the substituent, or the substituent) -- the benzene ring in which an oxygen atom or a sulfur atom may be shown, R2 may show the hydrocarbon group which may have the hydrogen atom or the substituent to, and Ring A may have the substituent -- in k, m shows the integer of 1-8 and n shows the integer of 1-6 for the integer of 0-3.] It comes out and they are the compound expressed and its salt. In said formula (I), the shape of a chain, annular, saturation, partial saturation, and the hydrocarbon group that consists of such various combination further are mentioned, for example as a "hydrocarbon group" of "the hydrocarbon group which may have the substituent" shown by R1 and R2. As a chain-like saturated hydrocarbon radical, the alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl) of the carbon numbers 1-11 (C 1-11) of the shape of the shape of a straight chain and branching is mentioned, for example. As a chain-like unsaturated hydrocarbon radical, the alkenyl radical (for example, vinyl, an allyl compound, 2-butenyl, isopropenyl) of C 2-4 of the shape of the shape of a straight chain and branching and the alkynyl group (an example, ethynyl, 2-propynyl, 2-butynyl, 3-butynyl) of C 2-4 are mentioned. As a cycloalkane radical, the monocycle cycloalkyl radical (for example, cyclo propyl, cyclo butyl, cyclopentyl, cyclohexyl) of C 3-7 and the bridge formation ring type saturated hydrocarbon radical (for example, bicyclo [3.2.1] oct-2-IRU and bicyclo [3.3.1] non -2-IRU, adamantane-1-IRU) of C 8-14 are mentioned. A phenyl group, a naphthyl group, etc. are used as an annular unsaturated hydrocarbon radical.

[0023] Moreover, the shape of a chain previously illustrated as the aforementioned "hydrocarbon group", annular, saturation, The hydrocarbon group which consists of various combination of the hydrocarbon group of partial saturation is sufficient. For example, seven to C18 aralkyl (for example, tolyl, xylyl; one to alpha-naphthyl-C8 alkyls, such as phenyl-C1-12 alkyl;alpha-naphthyl methyls, such as benzyl, phenethyl, phenylpropyl, phenyl butyl, phenyl pentyl, and phenyl hexyl), The C8-18 aryl alkenyl (for example, two to phenyl-C12 alkenyl, such as styryl, cinnamyl, 4-phenyl-2-butenyl, and 4-phenyl-3-butenyl), C8-18 aryl alkynyl (for example, two to phenyl-C12 alkynyl, such as phenethyl, 3-phenyl-2-propynyl, and 3-phenyl-1-propynyl), One to C3-7 cycloalkyl-C6 alkyl (for example) Cyclopropyl methyl, cyclo butyl methyl, cyclopentyl methyl, cyclohexyl methyl, cycloheptyl methyl, cyclo propylethyl, cyclo butyl ethyl, cyclopentyl ethyl, cyclohexyl ethyl, cycloheptyl ethyl, cyclo propyl butyl, Cyclo butyl butyl, cyclopentyl butyl, cyclohexyl butyl, cycloheptyl butyl, cyclo propyl pentyl, cyclo butyl pentyl, cyclopentyl pentyl, cyclohexyl pentyl, cycloheptyl pentyl, cyclo propyl hexyl, Cyclo butyl hexyl, cyclopentyl hexyl, cyclohexyl hexyl, cycloheptyl hexyl, etc. are mentioned.

[0024] As a "hydrocarbon group" of "the hydrocarbon group which may have the substituent" expressed with R1, the shape of a straight chain, branching-like C1-7 alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl), or a C7-10 aralkyl radical (for example, benzyl, phenethyl, phenylpropyl) is desirable also in the above. As a "hydrocarbon group" of "the hydrocarbon group which may have the

substituent" expressed with R2, C7-10 aralkyl (for example, benzyl, phenethyl, phenylpropyl) etc. is desirable also in the above. The above-mentioned hydrocarbon expressed with R1 and R2 may have the substituent in the replaceable location. As a substituent which chain-like saturation and chain-like partial saturation which are expressed with R1 and R2, and which were described above, and a cycloalkane radical may have For example, a halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy), C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical (For example, the alkyl carbonylamino whose alkyl parts, such as acetylamino, propionylamino, and butyryl amino, are C 1-4), A C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino, ethyl sulfonylamino), A C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl), A hydroxy carbonyl group, a C1-6 alkyl carbonyl group For example, (acetyl, a propionyl, the butyryl, valeryl, hepta-noil), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group For example, (N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl) etc. is mentioned, and you may have 1 chosen from these thru/or five pieces.

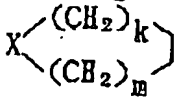
[0025] As the substituent of "the benzene ring which may have the substituent" expressed with Ring A in a formula (I), and a substituent of the annular unsaturated hydrocarbon radical expressed with R1 and R2 For example, C1-4 alkyl group (for example, methyl, ethyl, propyl, butyl), A halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy), C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, N-methylamino, N-ethylamino, N-propylamino, N, and N-dimethylamino, N, and N-diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical For example, (acetylamino, propionylamino, butyryl amino), An aminocarbonyl oxy-radical, monochrome, or a JI C1-4 alkyl carbamoyloxy radical For example, (N-methylcarbamoyloxy, N-ethyl carbamoyloxy, N, N-dimethylcarbamoyloxy, N,N-diethylcarbamoyloxy), a C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino —) Ethyl sulfonylamino, propyl sulfonylamino, a C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, iso butoxycarbonyl), A carboxy group, a C1-6 alkyl carbonyl group (for example, acetyl, a propionyl, butyryl, cyclohexyl carbonyl), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group (For example, N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl, N, and N-diethylcarbamoyl, N, and N-dibutyl carbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a cyclopentyl sulfonyl, a cyclohexyl sulfonyl), The phenyl which may have 1-4 substituents, naphthyl, phenoxy, Benzoyl, phenoxy carbonyl, phenyl C1-4 alkyl carbamoyl, Phenylcarbamoyl, phenyl C1-4 alkyl carbonylamino, Benzoylamino, a phenyl C1-4 alkyl sulfonyl, a phenyl sulfonyl, Phenyl C1-4 alkyl sulfinyl, phenyl C1-4 alkyl sulfonylamino, or a phenyl sulfonylamino radical (as a substituent in each phenyl group or naphthyl group) For example, C1-4 alkyl group, C1-4 alkoxy group which were illustrated above, halogen atoms, such as a fluorine, chlorine, a bromine, and iodine, a hydroxyl group, a benzyloxy radical, the amino group, monochrome or a JI C1-4 alkylamino radical, a nitro group, a C1-4 alkyl carbonyl group, etc. are used. etc. — it is mentioned. About 1-3 pieces are suitable for the number of the substituents of "the benzene ring which may have the substituent" expressed with these rings A, or the annular unsaturated hydrocarbon radical expressed with R1 and R2.

[0026] As a substituent of "the hydrocarbon group which consists of various combination of the shape of a chain, annular, saturation, and an unsaturated hydrocarbon radical" expressed with R1 and R2 For example, C1-4 alkyl group (for example, methyl, ethyl, propyl, butyl), A halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy),

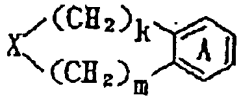
C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, N-methylamino, N-ethylamino, N-propylamino, N, and N-dimethylamino, N, and N-diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical For example, (acetylamino, propionylamino, butyryl amino), A carbamoyloxy radical, monochrome, or a JI C1-4 alkyl carbamoyloxy radical For example, (N-methylcarbamoyloxy, N-ethyl carbamoyloxy, N, N-dimethylcarbamoyloxy, N,N-diethylcarbamoyloxy), a C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino --) Ethyl sulfonylamino, propyl sulfonylamino, a C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, iso butoxycarbonyl), A hydroxy carbonyl group, a C1-6 alkyl carbonyl group For example, (acetyl, a propionyl, butyryl, cyclohexyl carbonyl), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group (For example, N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl, N, and N-diethylcarbamoyl, N, and N-dibutyl carbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a cyclopentyl sulfonyl, a cyclohexyl sulfonyl), The phenyl which may have 1-4 substituents, naphthyl, phenoxy, Benzoyl, phenoxy carbonyl, phenyl C1-4 alkyl carbamoyl, Phenylcarbamoyl, phenyl C1-4 alkyl carbonylamino, Benzoylamino, a phenyl C1-4 alkyl sulfonyl, a phenyl sulfonyl, Phenyl C1-4 alkyl sulfinyl, phenyl C1-4 alkyl sulfonylamino, or a phenyl sulfonylamino radical (as a substituent on each annular radical) For example, C1-4 alkyl groups, such as methyl, ethyl, propyl, butyl, and isopropyl, C1-4 alkoxy groups, such as methoxy and ethoxy , propyloxy, isopropyloxy, and butyloxy, halogen atoms, such as a fluorine, chlorine, a bromine, and iodine, a hydroxyl group, a benzyloxy radical, the amino group, the monochrome like the above or the JI C1-4 alkylation amino group, a nitro group, the C1-4 alkyl carbonyl group like the above, etc. are mentioned. etc. -- it is mentioned. About 1-5 pieces are suitable for the number of the permutations of these hydrocarbon groups.

[0027] As an "acyl group" of "the acyl group which may have the substituent" shown by R1 A carboxylic-acid acyl group (for example, C2-8 alkyl carbonyl or phenyl carbonyls, such as formyl, and acetyl, a propionyl, butyryl, benzoyl), a sulfonic-acid acyl group (for example, a methane sulfonyl, an ethane sulfonyl, and a propane sulfonyl --) A C1-7 alkyl sulfonyl or phenyl sulfonyls, such as benzenesulphonyl and p-tosyl, A phosphonic acid acyl group (for example, C1-7 alkyl phosphonyl, such as methane phosphonyl, ethane phosphonyl, propane phosphonyl, and benzene phosphonyl, or phenyl phosphonyl), A permutation oxy-carbonyl group (for example, C1-8 alkyloxy carbonyl or C7-8 aralkyloxy carbonyls, such as ethoxycarbonyl, tert-butoxycarbonyl, and benzyloxycarbonyl) is mentioned. Especially, a C2-8 alkyl carbonyl group is desirable. As a substituent which these acyl groups may have, Monod who has a halogen atom (for example, a fluorine, chlorine, a bromine, iodine), an amino group, and C1-6 alkyl group (for example, methyl, ethyl, propyl, hexyl) or a G alkylamino radical, C1-4 alkoxy group (for example, methoxy and ethoxy , propoxy), etc. are mentioned, and you may have 1-2 of these radicals preferably in 1-3 replaceable locations.

[0028] The desirable embodiment of a compound (it may only be written as a compound (I) among this description) expressed with a formula (I) is described below. as X -- R1-N -- < -- it is desirable and, as for cases, such as a hydrogen atom, the shape of a straight chain, branching-like C1-3 alkyl group (for example, methyl, ethyl, propyl, isopropyl), benzyl, phenyl, C1-4 alkyl carbonyl (for example, acetyl, a propionyl, butyryl), benzoyl, and C1-4 alkoxy carbonyl (for example, methoxycarbonyl, ethoxycarbonyl), R1 is more desirable especially. X -- especially -- desirable -- HN -- < -- it is . As R2, the benzyl or alpha-naphthyl methyl group permuted by no permuting or 1 thru/or two halogen atoms (for example, a fluorine, chlorine), methyl, nitroglycerine, and/or methoxy is desirable, and especially non-permuted benzyl is desirable. As a substituent on Ring A, a fluorine, chlorine, trifluoromethyl, methyl, methoxy, etc. are desirable, and especially a fluorine is desirable. Moreover, [Formula 2] when the sum (k+m) of k and m is the integer of 2-6



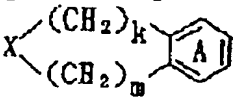
The case where five to ** 9 membered-ring is formed is desirable, and the case where k+m is 4 especially is desirable. As a combination of k and m, when k is 0, 2, 3, 4, or 5k is [m / ******] 1 and 1, 2, or 3 is [m / ****** / k] 2 again, as for m, 2 is still more desirable. Namely, [Formula 3]



(X=R¹-N<)

Come out and as nitrogen-containing condensation heterocycle expressed 2, 3-dihydro-1H-Indore, 1, 2, 3, 4-tetrahydroquinoline, 2, 3 and 4, 5-tetrahydro-1H-1-bends azepine, 2, a 3-dihydro-1H-iso indole, 1, 2 and 3, 4-tetrahydroisoquinoline, 2, 3, 4, 5-tetrahydro-1H-2-bends azepine, 2, 3 and 4, 5-tetrahydro-1H-3-bends azepine, 1, 2, 3, 4, 5, 6-hexahydro-1-bends azocine, 1, 2, 3, 4 and 5, 6-hexahydro-2-bends azocine, 1, 2, 3, 4, 5, 6-hexahydro-3-bends azocine, 2, 3, 4, 5 and 6, 7-hexahydro-1H-1-bends AZONIN, 2, 3, 4, 5, 6, 7-hexahydro-1H-2-bends AZONIN, 2, 3, 4, 5 and 6, 7-hexahydro-1H-3-bends AZONIN, 2, 3, 4, 5 and 6, and 7-hexahydro-1H-4-bends AZONIN is desirable. [0029]

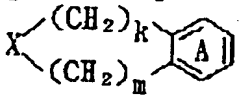
[Formula 4]



(X=O)

Come out and as oxygenated condensation heterocycle expressed 2, 3-dihydrobenzofuran, 1, 3-dihydroiso benzofuran, 3, 4-dihydro-2H-1-benzopyran, 3, 4-dihydro-1H-2-benzopyran, 2, 3 and 4, 5-tetrahydro-1-benzooxepin, 1, 3, 4, 5-tetrahydro-2-benzooxepin, 1, 2 and 4, 5-tetrahydro-3-benzooxepin, 3, 4, 5, 6-tetrahydro-2H-1-benzoOKISOSHIN, 3, 4 and 5, 6-tetrahydro-1H-2-benzoOKISOSHIN, 1, 4, 5, 6-tetrahydro-2H-3-benzoOKISOSHIN, 2, 3, 4, 5 and 6, 7-hexahydro-1-benzoOKISONIN, 1, 3, 4, 5, 6, 7-hexahydro-2-benzoOKISONIN, 1, 2, 4, 5 and 6, 7-hexahydro-3-benzoOKISONIN, 1, 2, 3, 5 and 6, and 7-hexahydro-4-benzoOKISONIN etc. is desirable. [0030]

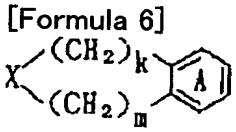
[Formula 5]



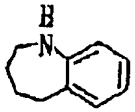
(X=S)

Come out and as sulfur-containing condensation heterocycle expressed 2, a 3-[dihydrob] thiophene, A 1 and 3-dihydrobenzo[c] thiophene, 3, 4-dihydro-2H-1-benzothiopyran, 3, 4-dihydro-1H-2-benzothiopyran, 2, 3 and 4, 5-tetrahydro-1-benzothiepine, 1, 3, 4, 5-tetrahydro-2-benzothiepine, 1, 2 and 4, 5-tetrahydro-3-benzothiepine, 3, 4, 5, 6-tetrahydro-2H-1-benzothiosin, 3, 4 and 5, 6-tetrahydro-1H-2-benzothiosin, 1, 4, 5, 6-tetrahydro-2H-3-benzothiosin, 2, 3, 4, 5 and 6, the 7-hexahydro-1-benzothionine, The 1, 3, 4, 5, 6, 7-hexahydro-2-benzothionine, 1, 2, 4, 5 and 6, 7-hexahydro-3-benzothionine, 1, 2, 3, 5 and 6, and 7-hexahydro-4-benzothionine etc. is desirable. [0031]

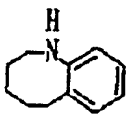
[Formula 6]



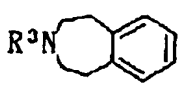
の好ましい縮合複素環としては、たとえば式



、



または



[-- R3 shows a hydrogen atom or C1-3 alkyl group among a formula.] It comes out, and it is the

nitrogen-containing condensation heterocycle expressed, and a bends azepine ring is especially desirable. The C1-3 alkyl groups shown by R3 are methyl, ethyl, propyl, and isopropyl among the above-mentioned formula. As for n, 1, 2 or 3, especially 2 are desirable. A compound (I) is 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine especially preferably.

[0032] The acid addition salt especially physiologically permitted as a salt of a compound (I) is desirable. As those salts, a salt with an inorganic acid (an example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, sulfuric acid) or a salt with an organic acid (an example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid) is mentioned, for example. Furthermore, when the compound (I) has acidic groups, such as -COOH, a compound (I) may form an inorganic base (an example, sodium, a potassium, calcium, magnesium, ammonia) or an organic base (an example, triethylamine), and a salt. The salt of a compound (I) is an organic-acid salt especially preferably. A compound (I) or its salt is 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine especially preferably. It is fumarate. A compound (I) or its salt is manufactured by JP,5-140149,A by the approach according to the well-known approach of a publication, or this, and is sold to it.

[0033] As the above-mentioned "pharmaceutical preparation component", for example The example of excipient [, a lactose, white soft sugar, D-mannitol, D-sorbitol, starch (corn starch, potatostarch, etc.), Pregelatinized starch, a dextrin, crystalline cellulose, hydroxypropylcellulose, Carboxymethylcellulose sodium, gum arabic, a dextran,], such as a pullulan, light anhydrous silicic acid, synthetic aluminum silicate, and magnesium aluminometasilicate, a binder (an example, pregelatinized starch, cane sugar, gelatin, and gum arabic powder --) Methyl cellulose, a carboxymethyl cellulose, carboxymethylcellulose sodium, Hydroxypropylcellulose, the hydroxypropyl methylcellulose, A polyvinyl pyrrolidone, crystalline cellulose, a dextrin, a pullulan, etc., lubricant (an example, magnesium stearate, and calcium stearate --) The example of disintegrator [, a lactose, white soft sugar, carboxymethyl celluloses, such as talc and a colloidal silica, hydroxypropylcellulose and starch (corn starch --)] and coloring agents, such as light anhydrous silicic acid, such as potatostarch, cross carmellose sodium, carboxy-methyl-starch sodium, and carboxymethyl-cellulose calcium, perfume, corrigent, an adsorbent, antiseptics, a wetting agent, an antistatic agent, a breaking extension agent, etc. are mentioned. The amount used for manufacture of common pharmaceutical preparation may be used for the addition of the above-mentioned pharmaceutical preparation component.

[0034] As dosage forms of the "remedy pharmaceutical preparation" of this invention, a tablet, a capsule, powder, a granule, a fine grain agent, a pill, etc. are mentioned, for example. A granule contains a particle with a particle size of about 177 micrometers or less for the particle of particle size 500 [about] - 1410 micrometers of abbreviation about 5 or less % of the weight about 90% of the weight or more. Moreover, a fine grain agent contains [the particle of particle size 10 / about / - 500 micrometers of abbreviation] a particle with a particle size of about 10 micrometers or less for a particle with a particle size of about 500 micrometers or more about 10 or less % of the weight about 5 or less % of the weight about 75% of the weight or more. A desirable fine grain agent contains [the particle of particle size 105 / about / - 500 micrometers of abbreviation] a particle with a particle size of about 74 micrometers or less for a particle with a particle size of about 500 micrometers or more about 10 or less % of the weight about 5 or less % of the weight about 75% of the weight or more.

[0035] The "remedy pharmaceutical preparation" of this invention is manufactured by covering with "coating" the "drug content constituent" which mixes "the above-mentioned drug" and above-mentioned "pharmaceutical preparation component" with a conventional method, and is obtained. What is necessary is just to choose the amount of the coating used according to the dosage forms of remedy pharmaceutical preparation. the amount of the coating (dry weight) used to remedy pharmaceutical preparation -- a tablet -- about 0.1- about 30 % of the weight -- desirable -- about 0.5- about 10 % of the weight -- it is --; granule and a pill -- about 0.1- about 50 % of the weight -- desirable -- about 1- about 20 % of the weight -- it is --; fine grain

agent -- about 0.1- about 100 % of the weight -- desirable -- about 1- it is about 50 % of the weight.
[0036] as the coat approach -- the very thing -- a well-known approach, for example, the pan coating method, a floating coating method, the approach that combined them with the rolling coating method pan are employable. Moreover, when coating is the solution or dispersion liquid containing water or an organic solvent, a spray coating method can also be adopted as the coat approach. The temperature in the case of a coat is usually about 25 - 40 degrees C of abbreviation preferably about 25 - 60 degrees C of abbreviation. Moreover, the time amount which a coat takes can be suitably chosen in consideration of the property of the coat approach and coating, the amount used, the property of remedy pharmaceutical preparation, etc.
[0037] The "remedy pharmaceutical preparation" of this invention can be used for prevention or the therapies of a disease, such as senile dementia, an Alzheimer disease, Huntington's chorea, motion fault polypathia, and mania, when using a compound (I) or its salt as a drug. What is necessary is just to choose the dose of the "remedy pharmaceutical preparation" of this invention in consideration of the class of drug, the class of object disease, a symptom, dosage forms, etc., so that the dose as a drug may turn into an effective dose of this drug. for example, the case where a compound (I) or its salt is used as a drug -- "remedy pharmaceutical preparation" -- the dose of a compound (I) or its salt -- an adult (weight of 60kg) -- setting -- about 0.01mg - about 100mg per day -- desirable -- about 0.1- about 30mg -- more -- desirable -- about 0.3- it is the range used as about 10mg, and a medicine is prescribed for the patient in 1 time or 2 - 3 steps.
[0038] Hereafter, the various kinds "remedy pharmaceutical preparation" of this invention are described concretely. "The stable remedy pharmaceutical preparation which it comes to cover with the protection-from-light agent which may generate a free radical by ultraviolet rays, and coating containing a free radical elimination agent" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the protection-from-light agent which may generate a free radical by ultraviolet rays", and a "free radical elimination agent." As for this coating, it is desirable to contain the oil further chosen from ester and alcohols. In this case, as for coating, it is desirable to contain an alkali further. Moreover, as this oil, a polyethylene glycol is desirable. As a suitable mode of ** "remedy pharmaceutical preparation", "the stable remedy pharmaceutical preparation which it comes to cover with coating containing (i) titanium oxide and (ii) sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol" is mentioned. Moreover, coating containing "the protection-from-light agent which may generate a free radical by ultraviolet rays", and a "free radical elimination agent" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0039] "The stable remedy pharmaceutical preparation which it comes to cover with the oil chosen from ester and alcohols and coating containing a free radical elimination agent" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the oil chosen from ester and alcohols", and a "free radical elimination agent." Moreover, coating containing "the oil chosen from ester and alcohols" and a "free radical elimination agent" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0040] "The stable remedy pharmaceutical preparation which it comes to cover with coating containing the oil chosen from ester and alcohols and an alkali" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the oil chosen from ester and alcohols", and a "alkali." As for this coating, it is desirable to contain the protection-from-light agent which may generate a free radical by ultraviolet rays further. Moreover, coating containing "the oil chosen from ester and alcohols" and a "alkali" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0041]
[Embodiment of the Invention] An example and the example of a trial explain this invention more concretely below.
[0042]

[Example] 2300g of example 1 purified water -- hydroxypropylmethylcellulose 2910 (TC-5) 129.6g and polyethylene glycol 6000 the free radical elimination agent which dissolves 30.0g and is shown in 20.0g of titanium oxide, 0.4g of yellow iron sesquioxides, and [a table 1], or an alkali (these are hereafter written as a stabilizing agent) -- 20.0g per sort was distributed, respectively and coating was manufactured, respectively.
[A table 1]

安定化剤
フリーラジカル消去剤
亜硫酸水素ナトリウム
アスコルビン酸
d-α-トコフェロール
塩基性物質
炭酸水素ナトリウム

[0043] In 2300g of water made from example dispermy, they are hydroxypropylmethylcellulose 2910 (TC-5) 121.6g and a polyethylene glycol 6000. 30.0g is dissolved, 20.0g of titanium oxide, 0.4g of yellow iron sesquioxides, 14.0g of sodium hydrogensulfites, and 14.0g of sodium hydrogencarbonates are distributed, and coating is manufactured.
[0044] In an example 3 fluid-bed granulation dryer (FD-3S and Powrex), they are 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine fumarate (hereafter). The water solution which dissolved hydroxypropylcellulose (HPC-L) 60.0g was sprayed and corned by the inside of a plane after mixing to homogeneity 40.0g, mannitol 1600g, and corn-starch 220.0g written as compound A, and, subsequently it dried in the fluid bed granulation dryer. Using the power mill grinder (P-3, the Showa chemical machinery machining place), the granulation object obtained was cracked on 1.5mmphi punching screen, and was made into the end of a particle size regulation. Furthermore, the same actuation as the above was repeated and the end of a particle size regulation was obtained. This end of a particle size regulation was taken 3456.0 g, 126.0 g corn starch and 18.0 g magnesium stearate were added to this, and it mixed with the tumbler mixer (TM-15, the Showa chemical machinery machining place), and considered as the granulation for making tablets. The making tablet (the tableting preassure of 0.8t / pestle) of this granulation was carried out by the weight of 100.0mg using the pestle of 6.5mmphi with the rotary tableting machine (correction 19K, Kikusui factory), and it considered as the naked tablet.
[0045] Film coated tablet 2800 locks each of a formula which spray various coating obtained in the example 1 on the naked tablet obtained, and contain 2.0mg of compound A per one lock in a film coating machine (HCT-20, Freund Industrial) in it and which are shown in [a table 2] were obtained.
[A table 2]
Tablet formula (presentation per one lock) : Group ** Loadings (mg) Compound A 2.0 D-mannitol 80.0 Corn starch 14.5 Hydroxypropylcellulose 3.0 Magnesium stearate 0.5 Total (naked tablet) 100.0 Naked tablet 100.0 (film component)
Hydroxypropylmethylcellulose 2910 2.592 A polyethylene glycol 6000 0.6 Titanium oxide 0.4 A yellow iron sesquioxide 0.008 Stabilizing agent 0.4 ** Total 104.0 [0046] A film coated tablet is manufactured like an example 3 except using coating manufactured in the example 2 as example 4 coating.
[0047] Not using example of comparison 1 stabilizing agent, the film coated tablet was manufactured like the example 3 except setting the amount of hydroxypropylmethylcellulose 2910 (TC-5) to 2.992mg per one lock.
[0048] The film coated tablet obtained in the stability assessment trial example 3 and the example 1 of a comparison of example of trial 1 film coated tablet was put into the plastics petri dish, and the top face of a petri dish was fixed with the polyvinylidene chloride film (Saran Wrap, Asahi Chemical Industry), and a bonnet and in order to seal thoroughly, the periphery of a petri

dish was fixed with the cellophane tape. this petri dish -- optical exposure [light source: -- by the following approaches, after time-amount (1000 lux x 50 days)] [dose:1,200,000 lux and, and] carrying out, a white fluorescent lamp and 1-methyl-8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, 5-tetrahydro-1H-1-bends azepine which are the decomposition product of compound A Fumarate (It is hereafter written as a decomposition product I) And the amount of generation of the formaldehyde which is the decomposition product of a polyethylene glycol was measured.
[the quantum approach of a decomposition product I] -- the conditions of the degree after dissolving by the mobile phase so that compound A may become in ml and about 200microg /, and filtering with a nonaqueous filter (0.45 micrometers) -- a high-speed liquid column chromatography (HPLC) -- the quantum was carried out by law. The amount of generation was expressed with the ratio with the initial content of compound A.
HPLC condition detector: Ultraviolet-rays absorptiometer and measurement wavelength:245nm column:TSK gel-80Ts, bore:4.6mm, die-length:150mm column temperature:40 degree-C mobile phase:0.05M potassium-dihydrogenphosphate solution (pH3.0)-acetonitrile mixture (volume ratio = 2:1)
flow rate: -- a part for 1ml/-- holding-time: -- [quantum approach of formaldehyde] tablet 5 lock is applied to 50ml distilled water for about 20 minutes, and it shakes for 30 minutes, and dissolves, and at-long-intervals alignment separation is carried out by 4000rpm for 10 minutes. The colorimetry (measurement wavelength of 550nm) of the filtrate which filters a supernatant with a drainage system filter (0.45 micrometers), and is obtained was carried out using the formaldehyde quantum kit (formaldehyde-Test Wako, Wako Pure Chem industry). In addition, the decomposition product I has the following physical properties.
chemical formula: -- C26H34N2O molecular weight: -- 390.267 [0049] A result is shown in [a table 3]. It is shown among a table that ND was not detected. The limit of detection of formaldehyde of the limit of detection of the decomposition product I which is a decomposition product of compound A is 4microg / lock 0.05%.
[A table 3]

	安定化剤	分解物Ｉの生成量 (%)	ホルムアルデヒド量 (μｇ／錠)
本発明	（実施例３）		
	亜硫酸水素ナトリウム	ＮＤ	６
	アスコルビン酸	ＮＤ	ＮＤ
	ｄ-α-トコフェロール	ＮＤ	６
	炭酸水素ナトリウム	ＮＤ	２４
対照	（比較例１）		
	なし	５．３	１３１

As shown in [a table 3], generation of a decomposition product I and formaldehyde was controlled by using a stabilizing agent. That is, by using coating containing titanium oxide, a polyethylene glycol 6000, and a stabilizing agent, decomposition of the compound A in the uncoated tablet covered with this coating was controlled, and the amount of generation of the formaldehyde which has an adverse effect on compound A was also controlled.
[0050] The assessment trial compound A, the titanium oxide, the polyethylene glycol 6000, corn starch, and stabilizing agent of the effect affect the compound A of example of trial 2 alkali or a free radical elimination agent were mixed so that a weight ratio might be set to 0.3:5:5:2.5:2.5, and powder was obtained. As a stabilizing agent, an alkali:sodium hydrogencarbonate, a sodium carbonate, a calcium carbonate, a magnesium carbonate, a magnesium hydroxide, or the free radical elimination agent:d-alpha-tocopherol was used. As contrast, powder was obtained like the above except using a stabilizing agent as corn starch. The powder obtained was put into the

glass petri dish, and the top face of a petri dish was fixed with the polyvinylidene chloride film (Saran Wrap, Asahi Chemical Industry), and a bonnet and in order to seal thoroughly, the periphery of a petri dish was fixed with the cellophane tape. this petri dish -- optical exposure [light source: -- a chemical lamp and after dose:350microwatt[/cm]2x five day] carrying out, the amount of generation of a decomposition product I was measured like the example 1 of a trial.
[0051] A result is shown in [a table 4].
[A table 4]

	安定化剤	分解物Iの生成量（%）
本発明	塩基性物質	
	炭酸水素ナトリウム	0．03
	炭酸ナトリウム	0．00
	炭酸カルシウム	0．00
	炭酸マグネシウム	0．00
	水酸化マグネシウム	0．00
	フリーラジカル消去剤	
	d-α-トコフェロール	0．00
対照	コーンスターチ	4．39

As shown in [a table 4], decomposition of compound A was controlled by adding an alkali or a free radical elimination agent to the powder containing compound A, titanium oxide, and a polyethylene glycol 6000.
[0052]
[Effect of the Invention] To light, division ultraviolet rays, or heat, the remedy pharmaceutical preparation of this invention is stable, and excellent in preservation stability. Moreover, since the front face of this remedy pharmaceutical preparation is uniform, processing of marking etc. is also easy and the result is also beautiful. Furthermore, as for this remedy pharmaceutical preparation, adhesion with esophageal mucous membrane is not seen at the time of administration. Coating of this invention is useful as a raw material for manufacturing the remedy pharmaceutical preparation which was excellent in preservation stability as mentioned above. Moreover, since this coating is excellent in reinforcement and plasticity, it is excellent in operability and a uniform coat is possible for it.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] To light (especially ultraviolet rays) or heat, this invention is stable and relates to the remedy pharmaceutical preparation excellent in preservation stability, and coating which is the raw material of such remedy pharmaceutical preparation.
[0002]
[Description of the Prior Art] When formaldehyde (the thing contained as an impurity of a polyethylene glycol 400 and the thing to produce according to air oxidation of a polyethylene glycol 400 are included) and an O6-benzyl guanine react, it is known that an O6-benzyl guanine will decompose in polyethylene-glycol 400 water solution and under a room temperature [the Pharma shoe CHIKARU research (Pharmaceutical Research), 11 volumes, No. 7, 1060 - 1064 pages, and 1994]. Performing enteric coating using the enteric film liquid containing titanium oxide and a polyethylene glycol 6000 is indicated by JP,63-301816,A (EP disclosure No. 0277741). Vitamin C, an in KYO (Yinqiao) extract, acetaminophen, Chlorpheniramine, a calcium carbonate, starch, a dextran, peppermint oil, The tablet which has the volatile oil of in KYO (Yinqiao) and a gin fan (jingfang) The hydroxypropyl methylcellulose, No2 The tablet covered with the component containing enteric vinyl resin, PEG6000, sesame oil, Tween 80, talc, titanium oxide, magnesium stearate, a hood color, 95% ethanol, and distilled water is chemical. The abs truck shoes It is indicated by 122:238853. JP,63-166824,A -- light -- the elastic capsule covered with the coating in which at least 85% contains the particle titanium oxide not more than particle diameter 0.1micrometer in the unstable drug content oleaginous solution is indicated.
[0003]
[Problem(s) to be Solved by the Invention] When providing a consumer with unstable remedy pharmaceutical preparation to light, it is necessary to perform a protection-from-light package or protection-from-light coat of remedy pharmaceutical preparation. However, if the state of preservation of the chemist's shop in a hospital or the remedy pharmaceutical preparation by the side of a patient is taken into consideration, it will be hard to say that the quality of remedy pharmaceutical preparation can be enough guaranteed by protection-from-light package. Therefore, when manufacturing unstable remedy pharmaceutical preparation to light, to perform a protection-from-light coat is desired. However, when coating which contains protection-from-light agents, such as titanium oxide, and plasticizers, such as a polyethylene glycol, on the occasion of pharmaceutical-preparation-izing of an unstable drug to light was covered to the drug content tablet, the trouble that the film coated tablet obtained was inferior to the tablet before performing coat processing in the stability over light became clear.
[0004]
[Means for Solving the Problem] When stabilization of the drug in the inside of a film coated tablet was considered in view of such a trouble, it found out that the titanium oxide in coating generates a free radical by 1 ultraviolet rays, that alcohols, such as a drug and a polyethylene glycol in coating, decompose with two free radicals, and that acids, such as aldehydes, such as the decomposition product of alcohols, such as a polyethylene glycol, for example, formaldehyde, and an acetaldehyde, and a formic acid, and a peroxide caused disassembly of a drug further in 3

coating. Based on such knowledge, the drug destabilization factor was canceled further, and this invention was completed, as a result of inquiring in order to obtain the remedy pharmaceutical preparation with which versatility was stabilized. That is, this invention is stable remedy pharmaceutical preparation which it comes to cover with the protection-from-light agent which may generate a free radical by (1) and (i) ultraviolet rays, and coating containing (ii) free radical elimination agent.;
(2) Remedy pharmaceutical preparation of the above-mentioned (1) publication with which coating comes to contain the oil further chosen from ester and alcohols;
(3) Remedy pharmaceutical preparation of the above-mentioned (1) publication whose protection-from-light agent which may generate a free radical by ultraviolet rays is a metallic oxide;
(4) Remedy pharmaceutical preparation of the above-mentioned (3) publication whose metallic oxide is titanium oxide, an iron sesquioxide, or a zinc oxide;
(5) Remedy pharmaceutical preparation of the above-mentioned (1) publication whose free radical elimination agent is a sulfite or vitamins;
(6) Vitamins are vitamin C or remedy pharmaceutical preparation given in vitamin-E above-mentioned [a certain] (5).;
(7) Remedy pharmaceutical preparation of the above-mentioned (2) publication whose oil is a polyethylene glycol;
(8) Stable remedy pharmaceutical preparation which it comes to cover with coating containing (i) titanium oxide and the (ii) sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol;
(9) Remedy pharmaceutical preparation of the above-mentioned (2) publication with which coating contains an alkali further;
(10) Remedy pharmaceutical preparation of the above-mentioned (9) publication whose alkali is a metaled carbonate or a metaled metal hydroxide.
(11) The oil chosen from (i) ester and alcohols, and stable remedy pharmaceutical preparation which it comes to cover with coating containing (ii) free radical elimination agent;
(12) The oil chosen from (i) ester and alcohols, and stable remedy pharmaceutical preparation which it comes to cover with coating containing the (ii) alkali;
(13) Remedy pharmaceutical preparation of the above (12) with which coating comes to contain the protection-from-light agent which may generate a free radical by ultraviolet rays further;
(14) The protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating characterized by containing (ii) free radical elimination agent;
(15) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with the protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating containing (ii) free radical elimination agent;
(16) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with the oil chosen from (i) ester and alcohols, and coating containing (ii) free radical elimination agent;
(17) The stabilization approach of the remedy pharmaceutical preparation characterized by covering a drug content constituent with coating containing the oil chosen from (i) ester and alcohols, and the (ii) alkali;
(18) Activity for remedy pharmaceutical preparation stabilization of the protection-from-light agent which may generate a free radical by (i) ultraviolet rays, and coating containing (ii) free radical elimination agent;
(19) It is related with the activity for remedy pharmaceutical preparation stabilization of coating containing the oil chosen from activity;, (20) (i) ester, and alcohols for remedy pharmaceutical preparation stabilization of the oil chosen from (i) ester and alcohols, and coating containing (ii) free radical elimination agent, and the (ii) alkali.
[0005] "The protection-from-light agent which may generate a free radical by ultraviolet rays" used for below in this invention, a "free radical elimination agent", "the oil chosen from ester and alcohols", a "alkali", "coating", and "remedy pharmaceutical preparation" are explained in full detail.

[0006] "The protection-from-light agent which may generate a free radical by ultraviolet rays" means what is added in remedy pharmaceutical preparation for the purpose of protection from light, and may generate a free radical by ultraviolet rays. Generally, these protection-from-light agent is ordinary temperature, and means what generates a free radical by exposing to the bottom of an indoor fluorescent lamp or outdoor daylight. As a free radical, O2, -, etc. are mentioned, for example. As such a protection-from-light agent, the oxide of inorganic substances, such as titanium oxide, an iron sesquioxide, and a zinc oxide, is mentioned, for example. A protection-from-light agent is a metallic oxide preferably, and titanium oxide still more preferably. Moreover, when using titanium oxide, the particle diameter is usually about 0.1 - 0.7 micrometers of abbreviation preferably about 0.01 - 1.5 micrometers of abbreviation. The contents in coating of "the protection-from-light agent which may generate a free radical by ultraviolet rays" are [that what is necessary is just the amount which can attain the object of protection from light of remedy pharmaceutical preparation] about 10 - 30 % of the weight of abbreviation preferably about 5 - 30 % of the weight of abbreviation.
[0007] A "free radical elimination agent" should just be matter which controls decomposition of the matter which can eliminate the above mentioned free radical and the coating component by oxidation reaction, or a remedy pharmaceutical preparation component. As a free radical elimination agent, for example Organic-acid; tryptophans [, such as an sugar-alcohol; benzoic acid], such as a mannitol, amino acid [, such as a cysteine,]; -- carbonate ion; -- metal complex; sodium hydrogensulfites, such as a copper complex and a manganese complex, -- Sulfites, such as a sodium sulfite and sodium metabisulfite; Sodium formaldehyde sulfoxylate (Rongalite), thiol derivative [, such as thioglycerol,]; -- natural resin [, such as guaiac resin,]; -- nordihydroguaiaretic acid -- Phenol derivatives, such as propyl gallate, burylhydroxyanisole, and dibutylhydroxytoluene; Erythorbic acid, sodium erythorbate and vitamin C (ascorbic acid ester, such as an example, ascorbyl palmitate, ascorbic-acid dipalmitate, and ascorbic-acid stearate, --) Ascorbic-acid salts, such as sodium ascorbate and calcium ascorbate, vitamin E (an example, the succinic-acid dl-alpha-tocopherol, the succinic-acid d-alpha-tocopherol, succinic-acid dl-alpha-tocopherol calcium, the acetic-acid dl-alpha-tocopherol, and the acetic-acid d-alpha-tocopherol --) The ester of tocopherols, such as nicotinic-acid dl-alpha-tocopherol Peptides [, such as a vitamin; glutathione], such as dl-alpha-tocopherol, d-alpha-tocopherol, a dl-delta-tocopherol, a d-delta-tocopherol, natural vitamin E, and beta carotene; pudding derivatives, such as a uric acid, etc. are mentioned. Two or more sorts may be mixed and used for these free radical elimination agents at one sort or a proper rate. A "free radical elimination agent" is a sulfite or vitamins (especially vitamin C and vitamin E) preferably, and is a sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol still more preferably. Moreover, in order to reinforce an operation of a "free radical elimination agent", ethylenediaminetetraacetic acid or its salt may be used together. The content in coating of a "free radical elimination agent" should just be an amount which can eliminate the free radical generated from the "protection-from-light agent which may generate a free radical by ultraviolet rays" contained in coating. The contents in coating of a "free radical elimination agent" are about 1 - 20 % of the weight of abbreviation preferably about 0.1 - 50 % of the weight of abbreviation.
[0008] as "the oil chosen from ester and alcohols" -- about 20- about 65 degrees C -- oil-like ester and alcohols -- polyhydric alcohol etc. is mentioned preferably. As this oil, the plasticizer usually used into remedy pharmaceutical preparation is mentioned, and, specifically, alcohols, such as ester; glycerols, such as citric-acid triethyl, a medium-chain-fatty-acid triglyceride, a diethyl phthalate, dibutyl phtalate, a triacetin (thoria cetyl glycerol), butyl phthalyl butyl glycolate, and glyceryl caprylic-acid ester, propylene glycol, and a polyethylene glycol, etc. are mentioned. In addition, sesame oil, castor oil, etc. can be used as oil. These oil may mix two or more sorts at one sort or a proper rate, and may be used. oil -- desirable -- alcohols -- more -- desirable -- polyhydric alcohol -- it is a polyethylene glycol especially preferably. Moreover, as a polyethylene glycol, a polyethylene glycol 400, a polyethylene glycol 600, a polyethylene glycol 1500, a polyethylene glycol 4000, a polyethylene glycol 6000, etc. are mentioned, for example. The contents in coating of oil are about 10 - 20 % of the weight of abbreviation preferably about

0.1 - 30 % of the weight of abbreviation. By adding the above-mentioned oil to coating, coating which was excellent in reinforcement and plasticity and was excellent in operability can be obtained. Moreover, a uniform coat is attained by using such coating.

[0009] That a "alkali" should just be matter in which the basicity which neutralizes acids, such as a formic acid, is shown specifically for example, the hydrogencarbonates (an example, sodium hydrogencarbonate, etc.) of alkali metal and the carbonate (an example --) of alkali metal the carbonate (an example --) of alkaline earth metal, such as a sodium carbonate and potassium carbonate a calcium carbonate, a magnesium carbonate, etc. -- etc. -- phosphoric-acid hydrogen 2 metaled salt (an example --) of carbonate; alkali metal disodium hydrogenphosphate, the potassium phosphate, etc. -- etc. -- phosphoric-acid hydrogen 2 -- a salt; calcium silicate -- silicates [, such as a magnesium silicate,]; -- metallic-oxides [, such as a magnesium oxide,]; -- a sodium hydroxide -- Tartrates, such as citrate;dl- [, such as a metal hydroxide; sodium citrate,], such as a calcium hydroxide, a magnesium hydroxide, and an aluminum hydroxide, and l-sodium tartrate; The salt which shows basicity, such as pantothenic acid salts, such as calcium pantothenate, An oxide or a hydroxide is mentioned. Two or more sorts may be mixed and used for these alkalis at one sort or a proper rate. An alkali is a metaled carbonate or a metaled metal hydroxide preferably, and are a sodium hydrogencarbonate, a sodium carbonate, potassium carbonate, a calcium carbonate, a magnesium carbonate, and a magnesium hydroxide still more preferably. Moreover, the contents in coating of an alkali are [that what is necessary is just sufficient amount to neutralize acids, such as a formic acid produced in remedy pharmaceutical preparation,] about 1 - 20 % of the weight of abbreviation preferably about 0.1 - 50 % of the weight of abbreviation.

[0010] "Coating" contains the coating basis other than the above-mentioned "protection-from-light agent which may generate a free radical by ultraviolet rays", a "free radical elimination agent", "the oil chosen from ester and alcohols", or a "alkali." The content in coating of this coating basis is an amount used for manufacture of common pharmaceutical preparation. Moreover, "coating" may contain further the additive which does not have an adverse effect on coating and remedy pharmaceutical preparation by request. Furthermore, "coating" may be the liquid which dissolved or distributed each above-mentioned component to water or an organic solvent. Especially the class of this organic solvent is not limited, for example, ketones [, such as an alcohols; acetone,], such as a methanol, ethanol, and isopropyl alcohol, can be used for it. Moreover, the mixed liquor of water and an organic solvent can also be used.

[0011] As the above-mentioned coating basis, a glycocalyx basis, a water-soluble film coating basis, an enteric film coating basis, a sustained-release film coating basis, etc. are mentioned, for example. As a glycocalyx basis, white soft sugar is used and one sort chosen from talc, a precipitated calcium carbonate, gelatin, gum arabic, a pullulan, a cull navarho, etc. or two sorts or more may be further used together. as a water-soluble film coating basis, polysaccharide [, such as a synthetic macromolecule; pullulan], such as cellulose type giant-molecule; polyvinyl-acetal diethylamino acetate, such as hydroxypropylcellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, and methyl hydroxyethyl cellulose, aminoalkylmetaacrylatecopolymer E [OIDORAGITTOE (trade name) and loam FARUMA], and a polyvinyl pyrrolidone, etc. is mentioned, for example. As an enteric film coating basis, it is the hydroxypropyl methylcellulose, for example. Phthalate, Hydroxypropyl methylcellulose Acetate succinate, Cellulose type macromolecules, such as carboxy methyl ethyl cellulose and cellulose acetate phthalate; Methacrylic acid copolymer L[OIDORAGITTOL (trade name) Loam FARUMA], methacrylic acid copolymer LD[OIDORAGITTO L-30D55 (trade name), Acrylic-acid system macromolecules, such as loam FARUMA] and methacrylic acid copolymer S [OIDORAGITTOS (trade name) and loam FARUMA]; natural products, such as a shellac, etc. are mentioned. As a sustained-release film coating basis, acrylic-acid system macromolecules, such as OIDORAGITTO RS (trade name) and cellulose type macromolecule [, such as ethyl cellulose,]; aminoalkylmetaacrylatecopolymer RS [loam FARUMA] ethyl-acrylate methacrylic acid methyl copolymer suspension [OIDORAGITTO NE (trade name) and loam FARUMA], etc. are mentioned, for example. Two or more sorts may be mixed and used for the above-mentioned coating basis at the proper rate.

[0012] As the above-mentioned additive, a coloring agent, perfume, etc. are mentioned, for

example and the addition is an amount used for manufacture of common pharmaceutical preparation. As a coloring agent, water-soluble edible tar dyes (an example, Food Red No.2 and No. 3, Food Yellow No.4 and No. 5, Food Blue No.1, No. 2, etc.), water-insoluble nature lake coloring matter (aluminum salt of said water-soluble edible tar dyes etc.), natural coloring matter (an example, beta carotene, chlorophyll, etc.), etc. are mentioned, for example. As perfume, lemon oil, Orange, dl-, or l-menthol is mentioned, for example.

[0013] "Coating" of this invention is manufactured by mixing, after adding the above-mentioned additive for each component, such as the above-mentioned "protection-from-light agent which may generate a free radical by ultraviolet rays", a "free radical elimination agent", "oil chosen from ester and alcohols", or a "alkali", and a coating basis by request. Moreover, "coating" is manufactured also by dissolving or distributing each above-mentioned component to water or the above-mentioned organic solvent, and can obtain a uniform coat by such manufacture approach.

[0014] The "remedy pharmaceutical preparation" of this invention is obtained by covering a "drug content constituent" with the above-mentioned coating. Even if ** "a drug content constituent" is "drug" independent, they may be a "drug" and mixture with the "pharmaceutical preparation component" of common use used for manufacture of remedy pharmaceutical preparation. As dosage forms of a drug content constituent, a tablet, powder, a granule, a fine grain agent, a pill, etc. are mentioned, for example.

[0015] The drug disassembled as a "drug" with light, the drug especially disassembled by ultraviolet rays, the drug disassembled with a free radical, the aldehydes (an example, formaldehyde, acetaldehyde) which a free radical decomposes a pharmaceutical preparation component and produces, acids (an example, formic acid), or a peroxide is mentioned. As such a drug, for example A nourishment strong preservative, an alleviation-of-fever painkilling antiphlogistic, A psychopharmaceutical, an anti-anxiety drug, an antidepressant, a sedative hypnotic, antispasmodic, a central nervous system acting drug, A brain metabolism improvement agent, an antiepiletic agent, a sympathomimetic drug, digestive medicine, antacid, antiulcer drug, Expectorant cough suppressant, antemetic, a respiratory accelerator, a bronchodilator, an antiallergic drug, An agent for dental and oral use, an antihistamine, cardiotonic, the agent for arrhythmia, diuretic, an antihypertensive, A vasoconstrictor, a coronary vasodilator, a peripheral vasodilator, antilipemic, a choleretic drug, One sort or two sorts or more of components chosen from an antibiotic, a chemotherapic drug, a diabetes-mellitus therapy agent, an osteoporosis therapy agent, a neuromuscular junction blocking drug, a ****** agent, a hormone drug, alkaloid system narcotics, sulfa drugs, the arthrifuge, the anticoagulant, the anticancer drug, the Alzheimer remedy, etc. are mentioned. The content in the "remedy pharmaceutical preparation" of these "a drug" should just be an effective dose of a "drug."

[0016] Hereafter, the example of the above-mentioned drug is described. As a nourishment strong preservative, mineral; proteins, such as vitamin A, vitamin D, vitamin E (acetic-acid d-alpha-tocopherol etc.), vitamins B1 (dibenzoyl thiamine, fursultiamine hydrochloride, etc.), vitamins B2 (riboflavin tetrabutyrate etc.), vitamins B6 (pyridoxine hydrochloride etc.), vitamin C, vitamin; calcium (an ascorbic acid, sodium L-ascorbate, etc.) of vitamins B12 (hydroxocobalamin acetate etc.), magnesium, and iron, amino acid, an oligosaccharide, a crude drug, etc. are mentioned, for example. As an alleviation-of-fever painkilling antiphlogistic, aspirin, acetaminophen, ethenzamide, ibuprofen, diphenhydramine hydrochloride, dl-chlorpheniramine maleate, dihydrocodeine phosphate, NOSUKABIN, methylephedrine hydrochloride, the phenylpropanolamine hydrochloride, caffeine, anhydrous caffeine, serrapeptase, lysozyme chloride, tolfenamic acid, mefenamic acid, diclofenac sodium, flufenamic acid, salicylamide, aminopyrine, ketoprofen, indomethacin, BUKORORU, pentazocine, etc. are mentioned, for example. As a psychopharmaceutical, chlorpromazine, reserpine, etc. are mentioned, for example. As an anti-anxiety drug, alprazolam, chlordiazepoxide, diazepam, etc. are mentioned, for example. As an antidepressant, imipramine, maprotiline, an amphetamine, etc. are mentioned, for example.

[0017] As a sedative hypnotic, estazolam, nitrazepam, diazepam, the perlapine, phenobarbital sodium, etc. are mentioned, for example. As antispasmodic, scopolamine hydrobromide, diphenhydramine hydrochloride, papaverine hydrochloride, etc. are mentioned, for example. As a

central nervous system acting drug, citicoline, ROCHIRENIN, etc. are mentioned, for example. As a brain metabolism improvement agent, IDEBENON, vinpocetine, hydrochloric-acid MEKUROFENIKISETO, 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine or its salt is mentioned, for example. As an antiepiletic agent, phenytoin, carbamazepine, etc. are mentioned, for example. As a sympathomimetic drug, isoproterenol hydrochloride etc. is mentioned, for example. As digestive medicine, medicines for intestinal disorders, such as stomachic digestive; hydrochloric-acid pel PERIN, such as diastase, saccharated pepsin, an extract of scopolia, cellulase AP 3, lipase AP, and cinnamon oil, antibiotics-resistant lactic acid bacteriae, and lactobacillus bifidus, etc. are mentioned, for example. As antacid, a magnesium carbonate, a sodium hydrogencarbonate, magnesium aluminometasilicate, synthetic hydrotalcite, a precipitated calcium carbonate, a magnesium oxide, etc. are mentioned, for example. As antiulcer drug, the Benz imidazole system compound (an example, lansoprazole, omeprazole, rabeprazole, punt PURAZORU), famotidine, cimetidine, ranitidine hydrochloride, etc. are mentioned, for example.

[0018] As expectorant cough suppressant, hydrochloric-acid cloperastine, a hydrobromic-acid DEKISUTORO melt fan, theophylline, a GUAYA call sulfonic-acid potassium, guaifenesin, codein phosphate, etc. are mentioned, for example. As antemetic, difenidol hydrochloride, metoclopramide, etc. are mentioned, for example. As a respiratory accelerator, levallorphan tartrate etc. is mentioned, for example. As a bronchodilator, theophylline, a sulfuric-acid ape butanol, etc. are mentioned, for example. As an antiallergic drug, amlexanox, seratrodast, etc. are mentioned, for example. As an agent for dental and oral use, oxytetracycline, triamcinolone acetonide, chlorhexidine hydrochloride, lidocaine, etc. are mentioned, for example. As an antihistamine, diphenhydramine hydrochloride, a promethazine, isothipendyl hydrochloride, dl-chlorpheniramine maleate, etc. are mentioned, for example. As cardiotonic, caffeine, digoxin, etc. are mentioned, for example. As an agent for arrhythmia, procainamide hydrochloride, propranolol hydrochloride, pindolol, etc. are mentioned, for example. As diuretic, iso SORUPIDO, furosemide, etc. are mentioned, for example. As an antihypertensive, they are delapril hydrochloride, captopril, a hexamethonium bromide, hydralazine hydrochloride, a hydrochloric-acid RAPETA roll, manidipine hydrochloride, and candesartan, for example. SHIREKI cetyl, methyldopa, a Losartan, valsartan, EPURO sultan, irbesartan, tasosartan, telmisartan, POMISARUTAN, RIPISARUTAN, FORA sultan, etc. are mentioned.

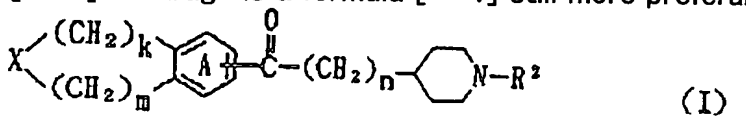
[0019] As vasoconstrictor, phenylephrine hydrochloride etc. is mentioned, for example. As a coronary vasodilator, carbocromen hydrochloride, molsidomine, hydrochloric-acid PERAPAMIRU, etc. are mentioned, for example. As a peripheral vasodilator, cinnarizine etc. is mentioned, for example. As antilipemic, auction bus TANCHIN sodium, simvastatin, PURABASUSUTACHIN, etc. are mentioned, for example. As a choleretic drug, dehydrocholic acid, TOREPIPUTON, etc. are mentioned, for example. As an antibiotic, monobactam antibiotic; penem system antibiotics [, such as synthetic-antimicrobials; carumonam sodium,], such as cephem antibiotic; ampicillins, such as cefalexin, amoxicillin, hydrochloric-acid PIPUMESHIRINAMU, cefotiam dihydrochloride, cefozopran hydrochloride, cefmenoxime hydrochloride, and cefsulodin sodium, SHIKURASHIN, sulbenicillin sodium, nalidixic acid, and enoxacin, a KARUPA penem system antibiotic, etc. are mentioned, for example. As a chemotherapic drug, hydrochloric-acid sulfamethizole, thiazosulfone, etc. are mentioned, for example. As a diabetes-mellitus therapy agent, tolbutamide, voglibose, a thiazolidinedione derivative (an example, pioglitazone hydrochloride, troglitazone, 5-[[4-[2-(methyl-2-pilus JINIRU amino) ethoxy] phenyl] methyl]-2, 4-thiazoline dione), acarbose, a MIGURI toll, EMIGURITETO, etc. are mentioned, for example. As an osteoporosis therapy agent, ipriflavone etc. is mentioned, for example. As a neuromuscular junction blocking drug, a METOKARUPA mall etc. is mentioned for example. As a ****** agent, the meclizine hydrochloride, cymene HIDORINATO, etc. are mentioned, for example.

[0020] As a hormone drug, RIOCHININ sodium, phosphoric-acid DEKIMETAZON sodium, prednisolone, oxendolone, leuprorelin acetate, etc. are mentioned, for example. As alkaloid system narcotics, opium, morphine hydrochloride, ipecac, oxycodone hydrochloride, opium alkaloids hydrochlorides, cocaine hydrochloride, etc. are mentioned, for example. As sulfa drugs, sulfamine, sulfamethizole, etc. are mentioned, for example. As arthrifuge, allopurinol, a colchicine,

etc. are mentioned, for example. As an anticoagulant, dicumarol is mentioned, for example. As an anticancer drug, 5-fluorouracil, a uracil, a mitomycin, etc. are mentioned, for example. As an Alzheimer disease remedy, IDEBENON, vinpocetine, 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine or its salt is mentioned, for example.

[0021] Moreover, since the aldehydes (the example, the formaldehyde, acetaldehyde), the acids (the example, formic acid), or the peroxide which ultraviolet rays, a free radical, or a free radical decomposes a pharmaceutical preparation component, and produces is easy to decompose, as for the "drug" which has an amino group or an imino group, it is desirable to use as a "drug" the "drug" which has an amino group or an imino group.

[0022] A "drug" is a formula [** 1] still more preferably.



(I)

the inside of [type, and X -- R1-N -- < (R1 shows the acyl group which may have the hydrocarbon group which may have the hydrogen atom and the substituent, or the substituent) -- the benzene ring in which an oxygen atom or a sulfur atom may be shown, R2 may show the hydrocarbon group which may have the hydrogen atom or the substituent to, and Ring A may have the substituent -- in k, m shows the integer of 1-8 and n shows the integer of 1-6 for the integer of 0-3.] It comes out and they are the compound expressed and its salt. In said formula (I), the shape of a chain, annular, saturation, partial saturation, and the hydrocarbon group that consists of such various combination further are mentioned, for example as a "hydrocarbon group" of "the hydrocarbon group which may have the substituent" shown by R1 and R2. As a chain-like saturated hydrocarbon radical, the alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl) of the carbon numbers 1-11 (C 1-11) of the shape of the shape of a straight chain and branching is mentioned, for example. As a chain-like unsaturated hydrocarbon radical, the alkenyl radical (for example, vinyl, an allyl compound, 2-butenyl, isopropenyl) of C 2-4 of the shape of the shape of a straight chain and branching and the alkynyl group (an example, ethynyl, 2-propynyl, 2-butynyl, 3-butynyl) of C 2-4 are mentioned. As a cycloalkane radical, the monocycle cycloalkyl radical (for example, cyclo propyl, cyclo butyl, cyclopentyl, cyclohexyl) of C 3-7 and the bridge formation ring type saturated hydrocarbon radical (for example, bicyclo [3.2.1] oct-2-IRU and bicyclo [3.3.1] non -2-IRU, adamantane-1-IRU) of C 8-14 are mentioned. A phenyl group, a naphthyl group, etc. are used as an annular unsaturated hydrocarbon radical.

[0023] Moreover, the shape of a chain previously illustrated as the aforementioned "hydrocarbon group", annular, saturation, The hydrocarbon group which consists of various combination of the hydrocarbon group of partial saturation is sufficient. For example, seven to C18 aralkyl (for example, tolyl, xylyl; one to alpha-naphthyl-C8 alkyls, such as phenyl-C1-12 alkyl;alpha-naphthyl methyls, such as benzyl, phenethyl, phenylpropyl, phenyl butyl, phenyl pentyl, and phenyl hexyl), The C8-18 aryl alkenyl (for example, two to phenyl-C12 alkenyl, such as styryl, cinnamyl, 4-phenyl-2-butenyl, and 4-phenyl-3-butenyl), C8-18 aryl alkynyl (for example, two to phenyl-C12 alkynyl, such as phenethyl, 3-phenyl-2-propynyl, and 3-phenyl-1-propynyl), One to C3-7 cycloalkyl-C6 alkyl (for example) Cyclopropyl methyl, cyclo butyl methyl, cyclopentyl methyl, cyclohexyl methyl, cycloheptyl methyl, cyclo propylethyl, cyclo butyl ethyl, cyclopentyl ethyl, cyclohexyl ethyl, cycloheptyl ethyl, cyclo propyl butyl, Cyclo butyl butyl, cyclopentyl butyl, cyclohexyl butyl, cycloheptyl butyl, cyclo propyl pentyl, cyclo butyl pentyl, cyclopentyl pentyl, cyclohexyl pentyl, cycloheptyl pentyl, cyclo propyl hexyl, Cyclo butyl hexyl, cyclopentyl hexyl, cyclohexyl hexyl, cycloheptyl hexyl, etc. are mentioned.

[0024] As a "hydrocarbon group" of "the hydrocarbon group which may have the substituent" expressed with R1, the shape of a straight chain, branching-like C1-7 alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl), or a C7-10 aralkyl radical (for example, benzyl, phenethyl, phenylpropyl) is desirable also in the above. As a "hydrocarbon group" of "the hydrocarbon group which may have the

substituent" expressed with R2, C7-10 aralkyl (for example, benzyl, phenethyl, phenylpropyl) etc. is desirable also in the above. The above-mentioned hydrocarbon expressed with R1 and R2 may have the substituent in the replaceable location. As a substituent which chain-like saturation and chain-like partial saturation which are expressed with R1 and R2, and which were described above, and a cycloalkane radical may have For example, a halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy), C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, methylamino, ethylamino, propylamino, dimethylamino, diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical (For example, the alkyl carbonylamino whose alkyl parts, such as acetylamino, propionylamino, and butyryl amino, are C 1-4), A C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino, ethyl sulfonylamino), A C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl), A hydroxy carbonyl group, a C1-6 alkyl carbonyl group For example, (acetyl, a propionyl, the butyryl, valeryl, hepta-noil), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group For example, (N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl) etc. is mentioned, and you may have 1 chosen from these thru/or five pieces.

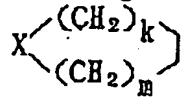
[0025] As the substituent of "the benzene ring which may have the substituent" expressed with Ring A in a formula (I), and a substituent of the annular unsaturated hydrocarbon radical expressed with R1 and R2 For example, C1-4 alkyl group (for example, methyl, ethyl, propyl, butyl), A halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy), C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, N-methylamino, N-ethylamino, N-propylamino, N, and N-dimethylamino, N, and N-diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical For example, (acetylamino, propionylamino, butyryl amino), An aminocarbonyl oxy-radical, monochrome, or a JI C1-4 alkyl carbamoyloxy radical For example, (N-methylcarbamoyloxy, N-ethyl carbamoyloxy, N, N-dimethylcarbamoyloxy, N,N-diethylcarbamoyloxy), a C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino —) Ethyl sulfonylamino, propyl sulfonylamino, a C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, iso butoxycarbonyl), A carboxy group, a C1-6 alkyl carbonyl group (for example, acetyl, a propionyl, butyryl, cyclohexyl carbonyl), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group (For example, N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl, N, and N-diethylcarbamoyl, N, and N-dibutyl carbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a cyclopentyl sulfonyl, a cyclohexyl sulfonyl), The phenyl which may have 1-4 substituents, naphthyl, phenoxy, Benzoyl, phenoxy carbonyl, phenyl C1-4 alkyl carbamoyl, Phenylcarbamoyl, phenyl C1-4 alkyl carbonylamino, Benzoylamino, a phenyl C1-4 alkyl sulfonyl, a phenyl sulfonyl, Phenyl C1-4 alkyl sulfinyl, phenyl C1-4 alkyl sulfonylamino, or a phenyl sulfonylamino radical (as a substituent in each phenyl group or naphthyl group) For example, C1-4 alkyl group, C1-4 alkoxy group which were illustrated above, halogen atoms, such as a fluorine, chlorine, a bromine, and iodine, a hydroxyl group, a benzyloxy radical, the amino group, monochrome or a JI C1-4 alkylamino radical, a nitro group, a C1-4 alkyl carbonyl group, etc. are used. etc. -- it is mentioned. About 1-3 pieces are suitable for the number of the substituents of "the benzene ring which may have the substituent" expressed with these rings A, or the annular unsaturated hydrocarbon radical expressed with R1 and R2.

[0026] As a substituent of "the hydrocarbon group which consists of various combination of the shape of a chain, annular, saturation, and an unsaturated hydrocarbon radical" expressed with R1 and R2 For example, C1-4 alkyl group (for example, methyl, ethyl, propyl, butyl), A halogen atom (for example, a fluorine, chlorine, a bromine, iodine), a nitro group, A cyano group, a hydroxy group, C1-4 alkoxy group (for example, methoxy and ethoxy , propyloxy, butyloxy, isopropyloxy),

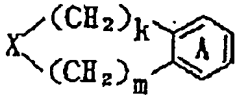
C1-4 alkylthio group (for example, a methylthio, ethyl thio, propyl thio, isopropyl thio, butyl thio), The amino group, monochrome, or a JI C1-4 alkylamino radical (for example, N-methylamino, N-ethylamino, N-propylamino, N, and N-dimethylamino, N, and N-diethylamino), The annular amino group (for example, pyrrolidino, piperidino), morpholino, a C1-4 alkyl carbonylamino radical For example, (acetylamino, propionylamino, butyryl amino), A carbamoyloxy radical, monochrome, or a JI C1-4 alkyl carbamoyloxy radical For example, (N-methylcarbamoyloxy, N-ethyl carbamoyloxy, N, N-dimethylcarbamoyloxy, N,N-diethylcarbamoyloxy), a C1-4 alkyl sulfonylamino radical (for example, methylsulfonylamino --) Ethyl sulfonylamino, propyl sulfonylamino, a C1-4 alkoxy carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxy carbonyl, iso butoxycarbonyl), A hydroxy carbonyl group, a C1-6 alkyl carbonyl group For example, (acetyl, a propionyl, butyryl, cyclohexyl carbonyl), A carbamoyl group, monochrome, or a JI C1-4 alkyl carbamoyl group (For example, N-methyl carbamoyl, N-ethyl carbamoyl, N-propyl carbamoyl, N-butylcarbamoyl, N, and N-diethylcarbamoyl, N, and N-dibutyl carbamoyl), A C1-6 alkyl sulfonyl group (for example, a methyl sulfonyl, an ethyl sulfonyl, a propyl sulfonyl, a cyclopentyl sulfonyl, a cyclohexyl sulfonyl), The phenyl which may have 1-4 substituents, naphthyl, phenoxy, Benzoyl, phenoxy carbonyl, phenyl C1-4 alkyl carbamoyl, Phenylcarbamoyl, phenyl C1-4 alkyl carbonylamino, Benzoylamino, a phenyl C1-4 alkyl sulfonyl, a phenyl sulfonyl, Phenyl C1-4 alkyl sulfinyl, phenyl C1-4 alkyl sulfonylamino, or a phenyl sulfonylamino radical (as a substituent on each annular radical) For example, C1-4 alkyl groups, such as methyl, ethyl, propyl, butyl, and isopropyl, C1-4 alkoxy groups, such as methoxy and ethoxy , propyloxy, isopropyloxy, and butyloxy, halogen atoms, such as a fluorine, chlorine, a bromine, and iodine, a hydroxyl group, a benzyloxy radical, the amino group, the monochrome like the above or the JI C1-4 alkylation amino group, a nitro group, the C1-4 alkyl carbonyl group like the above, etc. are mentioned. etc. -- it is mentioned. About 1-5 pieces are suitable for the number of the permutations of these hydrocarbon groups.

[0027] As an "acyl group" of "the acyl group which may have the substituent" shown by R1 A carboxylic-acid acyl group (for example, C2-8 alkyl carbonyl or phenyl carbonyls, such as formyl, and acetyl, a propionyl, butyryl, benzoyl), a sulfonic-acid acyl group (for example, a methane sulfonyl, an ethane sulfonyl, and a propane sulfonyl --) A C1-7 alkyl sulfonyl or phenyl sulfonyls, such as benzenesulphonyl and p-tosyl, A phosphonic acid acyl group (for example, C1-7 alkyl phosphonyl, such as methane phosphonyl, ethane phosphonyl, propane phosphonyl, and benzene phosphonyl, or phenyl phosphonyl), A permutation oxy-carbonyl group (for example, C1-8 alkyloxy carbonyl or C7-8 aralkyloxy carbonyls, such as ethoxycarbonyl, tert-butoxycarbonyl, and benzyloxycarbonyl) is mentioned. Especially, a C2-8 alkyl carbonyl group is desirable. As a substituent which these acyl groups may have, Monod who has a halogen atom (for example, a fluorine, chlorine, a bromine, iodine), an amino group, and C1-6 alkyl group (for example, methyl, ethyl, propyl, hexyl) or a G alkylamino radical, C1-4 alkoxy group (for example, methoxy and ethoxy , propoxy), etc. are mentioned, and you may have 1-2 of these radicals preferably in 1-3 replaceable locations.

[0028] The desirable embodiment of a compound (it may only be written as a compound (I) among this description) expressed with a formula (I) is described below. as X -- R1-N -- < -- it is desirable and, as for cases, such as a hydrogen atom, the shape of a straight chain, branching-like C1-3 alkyl group (for example, methyl, ethyl, propyl, isopropyl), benzyl, phenyl, C1-4 alkyl carbonyl (for example, acetyl, a propionyl, butyryl), benzoyl, and C1-4 alkoxy carbonyl (for example, methoxycarbonyl, ethoxycarbonyl), R1 is more desirable especially. X -- especially -- desirable -- HN -- < -- it is . As R2, the benzyl or alpha-naphthyl methyl group permuted by no permuting or 1 thru/or two halogen atoms (for example, a fluorine, chlorine), methyl, nitroglycerine, and/or methoxy is desirable, and especially non-permuted benzyl is desirable. As a substituent on Ring A, a fluorine, chlorine, trifluoromethyl, methyl, methoxy, etc. are desirable, and especially a fluorine is desirable. Moreover, [Formula 2] when the sum (k+m) of k and m is the integer of 2-6



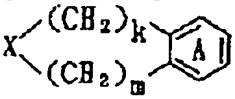
The case where five to ** 9 membered-ring is formed is desirable, and the case where k+m is 4 especially is desirable. As a combination of k and m, when k is 0, 2, 3, 4, or 5k is [m / ******] 1 and 1, 2, or 3 is [m / ****** / k] 2 again, as for m, 2 is still more desirable. Namely, [Formula 3]



(X=R¹-N<)

Come out and as nitrogen-containing condensation heterocycle expressed 2, 3-dihydro-1H-Indore, 1, 2, 3, 4-tetrahydroquinoline, 2, 3 and 4, 5-tetrahydro-1H-1-bends azepine, 2, a 3-dihydro-1H-iso indole, 1, 2 and 3, 4-tetrahydroisoquinoline, 2, 3, 4, 5-tetrahydro-1H-2-bends azepine, 2, 3 and 4, 5-tetrahydro-1H-3-bends azepine, 1, 2, 3, 4, 5, 6-hexahydro-1-bends azocine, 1, 2, 3, 4 and 5, 6-hexahydro-2-bends azocine, 1, 2, 3, 4, 5, 6-hexahydro-3-bends azocine, 2, 3, 4, 5 and 6, 7-hexahydro-1H-1-bends AZONIN, 2, 3, 4, 5, 6, 7-hexahydro-1H-2-bends AZONIN, 2, 3, 4, 5 and 6, 7-hexahydro-1H-3-bends AZONIN, 2, 3, 4, 5 and 6, and 7-hexahydro-1H-4-bends AZONIN is desirable. [0029]

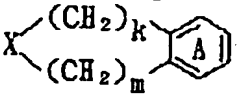
[Formula 4]



(X=O)

Come out and as oxygenated condensation heterocycle expressed 2, 3-dihydrobenzofuran, 1, 3-dihydroiso benzofuran, 3, 4-dihydro-2H-1-benzopyran, 3, 4-dihydro-1H-2-benzopyran, 2, 3 and 4, 5-tetrahydro-1-benzooxepin, 1, 3, 4, 5-tetrahydro-2-benzooxepin, 1, 2 and 4, 5-tetrahydro-3-benzooxepin, 3, 4, 5, 6-tetrahydro-2H-1-benzoOKISOSHIN, 3, 4 and 5, 6-tetrahydro-1H-2-benzoOKISOSHIN, 1, 4, 5, 6-tetrahydro-2H-3-benzoOKISOSHIN, 2, 3, 4, 5 and 6, 7-hexahydro-1-benzoOKISONIN, 1, 3, 4, 5, 6, 7-hexahydro-2-benzoOKISONIN, 1, 2, 4, 5 and 6, 7-hexahydro-3-benzoOKISONIN, 1, 2, 3, 5 and 6, and 7-hexahydro-4-benzoOKISONIN etc. is desirable. [0030]

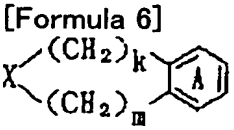
[Formula 5]



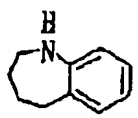
(X=S)

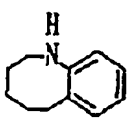
Come out and as sulfur-containing condensation heterocycle expressed 2, a 3-[dihydrob] thiophene, A 1 and 3-dihydrobenzo[c] thiophene, 3, 4-dihydro-2H-1-benzothiopyran, 3, 4-dihydro-1H-2-benzothiopyran, 2, 3 and 4, 5-tetrahydro-1-benzothiepine, 1, 3, 4, 5-tetrahydro-2-benzothiepine, 1, 2 and 4, 5-tetrahydro-3-benzothiepine, 3, 4, 5, 6-tetrahydro-2H-1-benzothiosin, 3, 4 and 5, 6-tetrahydro-1H-2-benzothiosin, 1, 4, 5, 6-tetrahydro-2H-3-benzothiosin, 2, 3, 4, 5 and 6, the 7-hexahydro-1-benzothionine, The 1, 3, 4, 5, 6, 7-hexahydro-2-benzothionine, 1, 2, 4, 5 and 6, 7-hexahydro-3-benzothionine, 1, 2, 3, 5 and 6, and 7-hexahydro-4-benzothionine etc. is desirable. [0031]

[Formula 6]

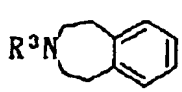


の好ましい縮合複素環としては、たとえば式





または



[-- R3 shows a hydrogen atom or C1-3 alkyl group among a formula.] It comes out, and it is the

nitrogen-containing condensation heterocycle expressed, and a bends azepine ring is especially desirable. The C1-3 alkyl groups shown by R3 are methyl, ethyl, propyl, and isopropyl among the above-mentioned formula. As for n, 1, 2 or 3, especially 2 are desirable. A compound (I) is 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine especially preferably.

[0032] The acid addition salt especially physiologically permitted as a salt of a compound (I) is desirable. As those salts, a salt with an inorganic acid (an example, a hydrochloric acid, a phosphoric acid, a hydrobromic acid, sulfuric acid) or a salt with an organic acid (an example, an acetic acid, a formic acid, a propionic acid, a fumaric acid, a maleic acid, a succinic acid, a tartaric acid, a citric acid, a malic acid, oxalic acid, a benzoic acid, methansulfonic acid, benzenesulfonic acid) is mentioned, for example. Furthermore, when the compound (I) has acidic groups, such as -COOH, a compound (I) may form an inorganic base (an example, sodium, a potassium, calcium, magnesium, ammonia) or an organic base (an example, triethylamine), and a salt. The salt of a compound (I) is an organic-acid salt especially preferably. A compound (I) or its salt is 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine especially preferably. It is fumarate. A compound (I) or its salt is manufactured by JP,5-140149,A by the approach according to the well-known approach of a publication, or this, and is sold to it.

[0033] As the above-mentioned "pharmaceutical preparation component", for example The example of excipient [, a lactose, white soft sugar, D-mannitol, D-sorbitol, starch (corn starch, potatostarch, etc.), Pregelatinized starch, a dextrin, crystalline cellulose, hydroxypropylcellulose, Carboxymethylcellulose sodium, gum arabic, a dextran,], such as a pullulan, light anhydrous silicic acid, synthetic aluminum silicate, and magnesium aluminometasilicate, a binder (an example, pregelatinized starch, cane sugar, gelatin, and gum arabic powder --) Methyl cellulose, a carboxymethyl cellulose, carboxymethylcellulose sodium, Hydroxypropylcellulose, the hydroxypropyl methylcellulose, A polyvinyl pyrrolidone, crystalline cellulose, a dextrin, a pullulan, etc., lubricant (an example, magnesium stearate, and calcium stearate --) The example of disintegrator [, a lactose, white soft sugar, carboxymethyl celluloses, such as talc and a colloidal silica, hydroxypropylcellulose and starch (corn starch --)] and coloring agents, such as light anhydrous silicic acid, such as potatostarch, cross carmellose sodium, carboxy-methyl-starch sodium, and carboxymethyl-cellulose calcium, perfume, corrigent, an adsorbent, antiseptics, a wetting agent, an antistatic agent, a breaking extension agent, etc. are mentioned. The amount used for manufacture of common pharmaceutical preparation may be used for the addition of the above-mentioned pharmaceutical preparation component.

[0034] As dosage forms of the "remedy pharmaceutical preparation" of this invention, a tablet, a capsule, powder, a granule, a fine grain agent, a pill, etc. are mentioned, for example. A granule contains a particle with a particle size of about 177 micrometers or less for the particle of particle size 500 [about] - 1410 micrometers of abbreviation about 5 or less % of the weight about 90% of the weight or more. Moreover, a fine grain agent contains [the particle of particle size 10 / about / - 500 micrometers of abbreviation] a particle with a particle size of about 10 micrometers or less for a particle with a particle size of about 500 micrometers or more about 10 or less % of the weight about 5 or less % of the weight about 75% of the weight or more. A desirable fine grain agent contains [the particle of particle size 105 / about / - 500 micrometers of abbreviation] a particle with a particle size of about 74 micrometers or less for a particle with a particle size of about 500 micrometers or more about 10 or less % of the weight about 5 or less % of the weight about 75% of the weight or more.

[0035] The "remedy pharmaceutical preparation" of this invention is manufactured by covering with "coating" the "drug content constituent" which mixes "the above-mentioned drug" and above-mentioned "pharmaceutical preparation component" with a conventional method, and is obtained. What is necessary is just to choose the amount of the coating used according to the dosage forms of remedy pharmaceutical preparation. the amount of the coating (dry weight) used to remedy pharmaceutical preparation -- a tablet -- about 0.1- about 30 % of the weight -- desirable -- about 0.5- about 10 % of the weight -- it is --; granule and a pill -- about 0.1- about 50 % of the weight -- desirable -- about 1- about 20 % of the weight -- it is --; fine grain

agent -- about 0.1- about 100 % of the weight -- desirable -- about 1- it is about 50 % of the weight.
[0036] as the coat approach -- the very thing -- a well-known approach, for example, the pan coating method, a floating coating method, the approach that combined them with the rolling coating method pan are employable. Moreover, when coating is the solution or dispersion liquid containing water or an organic solvent, a spray coating method can also be adopted as the coat approach. The temperature in the case of a coat is usually about 25 - 40 degrees C of abbreviation preferably about 25 - 60 degrees C of abbreviation. Moreover, the time amount which a coat takes can be suitably chosen in consideration of the property of the coat approach and coating, the amount used, the property of remedy pharmaceutical preparation, etc.
[0037] The "remedy pharmaceutical preparation" of this invention can be used for prevention or the therapies of a disease, such as senile dementia, an Alzheimer disease, Huntington's chorea, motion fault polypathia, and mania, when using a compound (I) or its salt as a drug. What is necessary is just to choose the dose of the "remedy pharmaceutical preparation" of this invention in consideration of the class of drug, the class of object disease, a symptom, dosage forms, etc., so that the dose as a drug may turn into an effective dose of this drug. for example, the case where a compound (I) or its salt is used as a drug -- "remedy pharmaceutical preparation" -- the dose of a compound (I) or its salt -- an adult (weight of 60kg) -- setting -- about 0.01mg - about 100mg per day -- desirable -- about 0.1- about 30mg -- more -- desirable -- about 0.3- it is the range used as about 10mg, and a medicine is prescribed for the patient in 1 time or 2 - 3 steps.
[0038] Hereafter, the various kinds "remedy pharmaceutical preparation" of this invention are described concretely. "The stable remedy pharmaceutical preparation which it comes to cover with the protection-from-light agent which may generate a free radical by ultraviolet rays, and coating containing a free radical elimination agent" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the protection-from-light agent which may generate a free radical by ultraviolet rays", and a "free radical elimination agent." As for this coating, it is desirable to contain the oil further chosen from ester and alcohols. In this case, as for coating, it is desirable to contain an alkali further. Moreover, as this oil, a polyethylene glycol is desirable. As a suitable mode of ** "remedy pharmaceutical preparation", "the stable remedy pharmaceutical preparation which it comes to cover with coating containing (i) titanium oxide and (ii) sodium hydrogensulfite, an ascorbic acid, sodium ascorbate, calcium ascorbate, dl-alpha-tocopherol, or the acetic-acid dl-alpha-tocopherol" is mentioned. Moreover, coating containing "the protection-from-light agent which may generate a free radical by ultraviolet rays", and a "free radical elimination agent" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0039] "The stable remedy pharmaceutical preparation which it comes to cover with the oil chosen from ester and alcohols and coating containing a free radical elimination agent" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the oil chosen from ester and alcohols", and a "free radical elimination agent." Moreover, coating containing "the oil chosen from ester and alcohols" and a "free radical elimination agent" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0040] "The stable remedy pharmaceutical preparation which it comes to cover with coating containing the oil chosen from ester and alcohols and an alkali" is manufactured by covering the above-mentioned "drug content constituent" with coating containing "the oil chosen from ester and alcohols", and a "alkali." As for this coating, it is desirable to contain the protection-from-light agent which may generate a free radical by ultraviolet rays further. Moreover, coating containing "the oil chosen from ester and alcohols" and a "alkali" is manufactured by dissolving or distributing these components to purified water with a coating basis, for example.
[0041]
[Embodiment of the Invention] An example and the example of a trial explain this invention more concretely below.
[0042]

[Example] 2300g of example 1 purified water -- hydroxypropylmethylcellulose 2910 (TC-5) 129.6g and polyethylene glycol 6000 the free radical elimination agent which dissolves 30.0g and is shown in 20.0g of titanium oxide, 0.4g of yellow iron sesquioxides, and [a table 1], or an alkali (these are hereafter written as a stabilizing agent) -- 20.0g per sort was distributed, respectively and coating was manufactured, respectively.
[A table 1]

安定化剤
フリーラジカル消去剤
亜硫酸水素ナトリウム
アスコルビン酸
d-α-トコフェロール
塩基性物質
炭酸水素ナトリウム

[0043] In 2300g of water made from example dispermy, they are hydroxypropylmethylcellulose 2910 (TC-5) 121.6g and a polyethylene glycol 6000. 30.0g is dissolved, 20.0g of titanium oxide, 0.4g of yellow iron sesquioxides, 14.0g of sodium hydrogensulfites, and 14.0g of sodium hydrogencarbonates are distributed, and coating is manufactured.
[0044] In an example 3 fluid-bed granulation dryer (FD-3S and Powrex), they are 8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, and 5-tetrahydro-1H-1-bends azepine fumarate (hereafter). The water solution which dissolved hydroxypropylcellulose (HPC-L) 60.0g was sprayed and corned by the inside of a plane after mixing to homogeneity 40.0g, mannitol 1600g, and corn-starch 220.0g written as compound A, and, subsequently it dried in the fluid bed granulation dryer. Using the power mill grinder (P-3, the Showa chemical machinery machining place), the granulation object obtained was cracked on 1.5mmphi punching screen, and was made into the end of a particle size regulation. Furthermore, the same actuation as the above was repeated and the end of a particle size regulation was obtained. This end of a particle size regulation was taken 3456.0 g, 126.0 g corn starch and 18.0 g magnesium stearate were added to this, and it mixed with the tumbler mixer (TM-15, the Showa chemical machinery machining place), and considered as the granulation for making tablets. The making tablet (the tableting preassure of 0.8t / pestle) of this granulation was carried out by the weight of 100.0mg using the pestle of 6.5mmphi with the rotary tableting machine (correction 19K, Kikusui factory), and it considered as the naked tablet.
[0045] Film coated tablet 2800 locks each of a formula which spray various coating obtained in the example 1 on the naked tablet obtained, and contain 2.0mg of compound A per one lock in a film coating machine (HCT-20, Freund Industrial) in it and which are shown in [a table 2] were obtained.
[A table 2]
Tablet formula (presentation per one lock) : Group ** Loadings (mg) Compound A 2.0 D-mannitol 80.0 Corn starch 14.5 Hydroxypropylcellulose 3.0 Magnesium stearate 0.5 Total (naked tablet) 100.0 Naked tablet 100.0 (film component)
Hydroxypropylmethylcellulose 2910 2.592 A polyethylene glycol 6000 0.6 Titanium oxide 0.4 A yellow iron sesquioxide 0.008 Stabilizing agent 0.4 ** Total 104.0 [0046] A film coated tablet is manufactured like an example 3 except using coating manufactured in the example 2 as example 4 coating.
[0047] Not using example of comparison 1 stabilizing agent, the film coated tablet was manufactured like the example 3 except setting the amount of hydroxypropylmethylcellulose 2910 (TC-5) to 2.992mg per one lock.
[0048] The film coated tablet obtained in the stability assessment trial example 3 and the example 1 of a comparison of example of trial 1 film coated tablet was put into the plastics petri dish, and the top face of a petri dish was fixed with the polyvinylidene chloride film (Saran Wrap, Asahi Chemical Industry), and a bonnet and in order to seal thoroughly, the periphery of a petri

dish was fixed with the cellophane tape. this petri dish -- optical exposure [light source: -- by the following approaches, after time-amount (1000 lux x 50 days)] [dose:1,200,000 lux and, and] carrying out, a white fluorescent lamp and 1-methyl-8-[1-oxo--3-[1-(phenylmethyl) piperidine-4-IRU] propyl]-2, 3 and 4, 5-tetrahydro-1H-1-bends azepine which are the decomposition product of compound A Fumarate (It is hereafter written as a decomposition product I) And the amount of generation of the formaldehyde which is the decomposition product of a polyethylene glycol was measured.
[the quantum approach of a decomposition product I] -- the conditions of the degree after dissolving by the mobile phase so that compound A may become in ml and about 200microg /, and filtering with a nonaqueous filter (0.45 micrometers) -- a high-speed liquid column chromatography (HPLC) -- the quantum was carried out by law. The amount of generation was expressed with the ratio with the initial content of compound A.
HPLC condition detector: Ultraviolet-rays absorptiometer and measurement wavelength:245nm column:TSK gel-80Ts, bore:4.6mm, die-length:150mm column temperature:40 degree-C mobile phase:0.05M potassium-dihydrogenphosphate solution (pH3.0)-acetonitrile mixture (volume ratio = 2:1)
flow rate: -- a part for 1ml/-- holding-time: -- [quantum approach of formaldehyde] tablet 5 lock is applied to 50ml distilled water for about 20 minutes, and it shakes for 30 minutes, and dissolves, and at-long-intervals alignment separation is carried out by 4000rpm for 10 minutes. The colorimetry (measurement wavelength of 550nm) of the filtrate which filters a supernatant with a drainage system filter (0.45 micrometers), and is obtained was carried out using the formaldehyde quantum kit (formaldehyde-Test Wako, Wako Pure Chem industry). In addition, the decomposition product I has the following physical properties.
chemical formula: -- C26H34N2O molecular weight: -- 390.267 [0049] A result is shown in [a table 3]. It is shown among a table that ND was not detected. The limit of detection of formaldehyde of the limit of detection of the decomposition product I which is a decomposition product of compound A is 4microg / lock 0.05%.
[A table 3]

	安定化剤	分解物Ｉの生成量 (%)	ホルムアルデヒド量 (μg／錠)
本発明	（実施例３）		
	亜硫酸水素ナトリウム	ＮＤ	６
	アスコルビン酸	ＮＤ	ＮＤ
	d-α-トコフェロール	ＮＤ	６
	炭酸水素ナトリウム	ＮＤ	２４
対照	（比較例１）		
	なし	５．３	１３１

As shown in [a table 3], generation of a decomposition product I and formaldehyde was controlled by using a stabilizing agent. That is, by using coating containing titanium oxide, a polyethylene glycol 6000, and a stabilizing agent, decomposition of the compound A in the uncoated tablet covered with this coating was controlled, and the amount of generation of the formaldehyde which has an adverse effect on compound A was also controlled.
[0050] The assessment trial compound A, the titanium oxide, the polyethylene glycol 6000, corn starch, and stabilizing agent of the effect affect the compound A of example of trial 2 alkali or a free radical elimination agent were mixed so that a weight ratio might be set to 0.3:5:5:2.5:2.5, and powder was obtained. As a stabilizing agent, an alkali:sodium hydrogencarbonate, a sodium carbonate, a calcium carbonate, a magnesium carbonate, a magnesium hydroxide, or the free radical elimination agent:d-alpha-tocopherol was used. As contrast, powder was obtained like the above except using a stabilizing agent as corn starch. The powder obtained was put into the

glass petri dish, and the top face of a petri dish was fixed with the polyvinylidene chloride film (Saran Wrap, Asahi Chemical Industry), and a bonnet and in order to seal thoroughly, the periphery of a petri dish was fixed with the cellophane tape. this petri dish -- optical exposure [light source: -- a chemical lamp and after dose:350microwatt[/cm]2x five day] carrying out, the amount of generation of a decomposition product I was measured like the example 1 of a trial.
[0051] A result is shown in [a table 4].
[A table 4]

	安定化剤	分解物Iの生成量（%）
本発明	塩基性物質	
	炭酸水素ナトリウム	0．03
	炭酸ナトリウム	0．00
	炭酸カルシウム	0．00
	炭酸マグネシウム	0．00
	水酸化マグネシウム	0．00
	フリーラジカル消去剤	
	d-α-トコフェロール	0．00
対照	コーンスターチ	4．39

As shown in [a table 4], decomposition of compound A was controlled by adding an alkali or a free radical elimination agent to the powder containing compound A, titanium oxide, and a polyethylene glycol 6000.
[0052]
[Effect of the Invention] To light, division ultraviolet rays, or heat, the remedy pharmaceutical preparation of this invention is stable, and excellent in preservation stability. Moreover, since the front face of this remedy pharmaceutical preparation is uniform, processing of marking etc. is also easy and the result is also beautiful. Furthermore, as for this remedy pharmaceutical preparation, adhesion with esophageal mucous membrane is not seen at the time of administration. Coating of this invention is useful as a raw material for manufacturing the remedy pharmaceutical preparation which was excellent in preservation stability as mentioned above. Moreover, since this coating is excellent in reinforcement and plasticity, it is excellent in operability and a uniform coat is possible for it.

[Translation done.]